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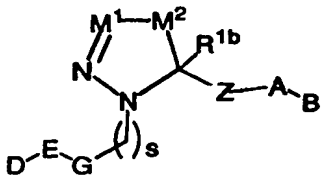
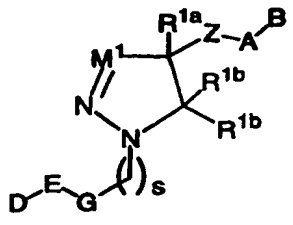


(I)



(II)

(57) Abstract

The present application describes disubstituted pyrazolines and triazolines of formulae (I) and (II), or pharmaceutically acceptable salt forms thereof, wherein one of M^1 and M^2 may be N and D may be a variety of N–containing groups, which are useful as inhibitors of factor Xa.

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TITLE

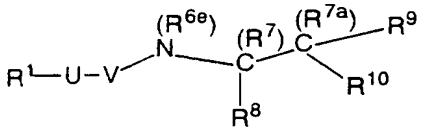
DISUBSTITUTED PYRAZOLINES AND TRIAZOLINES AS FACTOR XA INHIBITORS

FIELD OF THE INVENTION

This invention relates generally to disubstituted pyrazolines and triazolines which are inhibitors of trypsin-like serine protease enzymes, especially factor Xa, pharmaceutical compositions containing the same, and methods of using the same as anticoagulant agents for treatment and prevention of thromboembolic disorders.

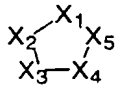
BACKGROUND OF THE INVENTION

WO 95/18111 addresses fibrinogen receptor antagonists, containing basic and acidic termini, of the formula:



wherein R^1 represents the basic termini, U is an alkylene or heteroatom linker, V may be a heterocycle, and the right hand portion of the molecule represents the acidic termini. The presently claimed compounds do not contain the acidic termini of WO 95/18111.

In U.S. Patent No. 5,463,071, Himmelsbach et al depict cell aggregation inhibitors which are 5-membered heterocycles of the formula:



wherein the heterocycle may be aromatic and groups A-B-C- and F-E-D- are attached to the ring system. A-B-C- can be a wide variety of substituents including a basic group attached to an aromatic ring. The F-E-D- group, however, would appear to be an acidic functionality which differs from the present

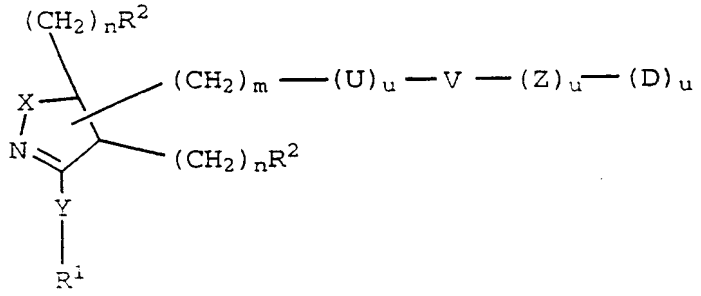
invention. Furthermore, use of these compounds as inhibitors of factor Xa is not discussed.

WO 97/47299 describes amidino and guanidino heterocyclic protease inhibitors of the formula:

$$R^1\text{-}Z\text{-}X\text{-}Y\text{-}W$$

wherein W contains an amidino, guanidino, or imino group attached to a variety of moieties including phenyl and piperidinyl, Y is a O, N, S, or C linker or is absent, X is a heterocycle, Z is a two atom linker containing at least one heteroatom, and R^1 is a variety of groups including cycloalkyl, aryl, heteroaryl, and araalkyl all of which are optionally substituted. A variety of proteases are described as possible targets for these compounds including Factor Xa. The presently claimed compounds differ in that they do not contain the combination R^1-Z or Y-W.

WO 97/23212 describes isoxazolines, isothiazolines, and pyrazolines of the formula:



wherein X is O, S or NR^{15}. Though the pyrazolines of WO 97/23212 are indicated to be factor Xa inhibitors, they are not considered part of the present invention.

Activated factor Xa, whose major practical role is the generation of thrombin by the limited proteolysis of prothrombin, holds a central position that links the intrinsic and extrinsic activation mechanisms in the final common pathway of blood coagulation. The generation of thrombin, the final serine protease in the pathway to generate a fibrin clot, from its precursor is amplified by formation of prothrombinase complex (factor Xa, factor V, Ca^{2+} and phospholipid). Since it is calculated that one molecule of

factor Xa can generate 138 molecules of thrombin (Elodi, S., Varadi, K.: *Optimization of conditions for the catalytic effect of the factor IXa-factor VIII Complex: Probable role of the complex in the amplification of blood coagulation.* *Thromb. Res.* **1979**, *15*, 617-629), inhibition of factor Xa may be more efficient than inactivation of thrombin in interrupting the blood coagulation system.

Therefore, efficacious and specific inhibitors of factor Xa are needed as potentially valuable therapeutic agents for the treatment of thromboembolic disorders. It is thus desirable to discover new factor Xa inhibitors.

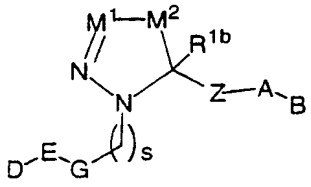
SUMMARY OF THE INVENTION

Accordingly, one object of the present invention is to provide novel disubstituted pyrazolines and triazolines which are useful as factor Xa inhibitors or pharmaceutically acceptable salts or prodrugs thereof.

It is another object of the present invention to provide pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

It is another object of the present invention to provide a method for treating thromboembolic disorders comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

These and other objects, which will become apparent during the following detailed description, have been achieved by the inventors' discovery that compounds of formulae I and II:



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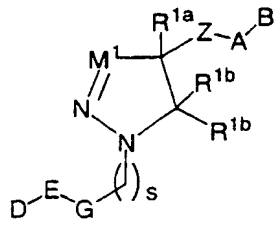
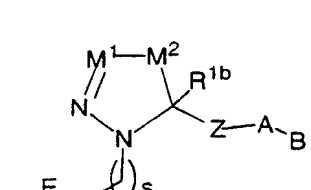


II

or pharmaceutically acceptable salt or prodrug forms thereof, wherein A, B, D, E, G, M, Z, R^{1a}, R^{1b}, and s are defined below, are effective factor Xa inhibitors.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[1] Thus, in a first embodiment, the present invention provides novel compounds of formulae I or II:



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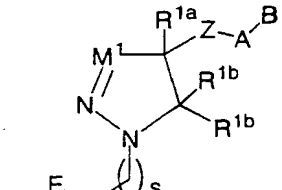


II

or a stereoisomer or pharmaceutically acceptable salt thereof, wherein;

M^1 is N or CR^{1c};

M^2 is NR^{1a} or $CR^{1a}R^{1a}$, provided that only one of M^1 and M^2 is a N atom;

D is selected from $C(=NR^8)NR^7R^9$, $NHC(=NR^8)NR^7R^9$, $NR^8CH(=NR^7)$, $C(O)NR^7R^8$, and $CR^8R^9NR^7R^8$;

E is selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, and piperidinyl substituted with 1 R;

alternatively, D-E-G together represent pyridyl substituted with 1 R;

R is selected from H, Cl, F, Br, I, $(CH_2)_tOR^3$, C_{1-4} alkyl, OCF_3, CF_3, $C(O)NR^7R^8$, and $(CR^8R^9)_tNR^7R^8$;

G is selected from $NHCH_2$, OCH_2, and SCH_2, provided that when s is 0, then G is absent;

Z is selected from a C_{1-4} alkylene, $(CH_2)_rO(CH_2)_r$, $(CH_2)_rNR^3(CH_2)_r$, $(CH_2)_rC(O)(CH_2)_r$, $(CH_2)_rC(O)O(CH_2)_r$, $(CH_2)_rOC(O)(CH_2)_r$, $(CH_2)_rC(O)NR^3(CH_2)_r$, $(CH_2)_rNR^3C(O)(CH_2)_r$, $(CH_2)_rOC(O)O(CH_2)_r$, $(CH_2)_rOC(O)NR^3(CH_2)_r$, $(CH_2)_rNR^3C(O)O(CH_2)_r$, $(CH_2)_rNR^3C(O)NR^3(CH_2)_r$, $(CH_2)_rS(O)_p(CH_2)_r$, $(CH_2)_rSO_2NR^3(CH_2)_r$, $(CH_2)_rNR^3SO_2(CH_2)_r$, and $(CH_2)_rNR^3SO_2NR^3(CH_2)_r$, provided that Z does not form a N-N, N-O, N-S, NCH_2N, NCH_2O, or NCH_2S bond with group A;

R^{1a} and R^{1b} are, at each occurrence, independently selected from H, $-(CH_2)_r-R^{1'}$, $NCH_2R^{1''}$, $OCH_2R^{1''}$, $SCH_2R^{1''}$, $N(CH_2)_2(CH_2)_tR^{1'}$, $O(CH_2)_2(CH_2)_tR^{1'}$, and $S(CH_2)_2(CH_2)_tR^{1'}$;

R^{1c} is selected from H, $-(CH_2)_q-R^{1'}$, C_{1-3} alkyl, $C(O)R^{2c}$, $(CF_2)_rCO_2R^{2c}$, $C(O)NR^2R^{2a}$, C_{3-6} carbocyclic residue substituted with 0-2 R^4, and 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^4;

$R^{1'}$ is selected from H, C_{1-3} alkyl, halo, $(CF_2)_rCF_3$, OR^2, NR^2R^{2a}, $C(O)R^{2c}$, $OC(O)R^2$, $(CF_2)_rCO_2R^{2c}$, $S(O)_pR^{2b}$, $NR^2(CH_2)_rOR^2$, $NR^2C(O)R^{2b}$, $NR^2C(O)NHR^{2b}$, $NR^2C(O)_2R^{2a}$, $OC(O)NR^{2b}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2R^{2b}$, C_{3-6} carbocyclic residue substituted with 0-2 R^4, and 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^4;

$R^{1''}$ is selected from H, $C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $S(O)R^{2b}$, $S(O)_2R^{2b}$, and $SO_2NR^2R^{2a}$;

R^2, at each occurrence, is selected from H, CF_3, C_{1-6} alkyl, benzyl, C_{3-6} carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

R^{2a}, at each occurrence, is selected from H, CF_3, C_{1-6} alkyl, benzyl, C_{3-6} carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

R^{2b}, at each occurrence, is selected from CF_3, C_{1-4} alkoxy, C_{1-6} alkyl, benzyl, C_{3-6} carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

R^{2c}, at each occurrence, is selected from CF_3, OH, C_{1-4} alkoxy, C_{1-6} alkyl, benzyl, C_{3-6} carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

alternatively, R^2 and R^{2a} combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring substituted with 0-2 R^{4b} which contains from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

R^3, at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

R^{3a}, at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

A is selected from:

C_{3-10} carbocyclic residue substituted with 0-2 R^4, and

5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^4;

B is selected from:

X-Y, NR^2R^{2a}, $C(=NR^2)NR^2R^{2a}$, $NR^2C(=NR^2)NR^2R^{2a}$,

C_{3-10} carbocyclic residue substituted with 0-2 R^{4a}, and

5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a};

X is selected from C_{1-4} alkylene, $-CR^2(CR^2R^{2b})(CH_2)_t-$, $-C(O)-$, $-C(=NR)-$, $-CR^2(NR^{1''}R^2)-$, $-CR^2(OR^2)-$, $-CR^2(SR^2)-$, $-C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)$, $-S(O)_p-$, $-S(O)_pCR^2R^{2a}-$, $-CR^2R^{2a}S(O)_p-$, $-S(O)_2NR^2-$, $-NR^2S(O)_2-$, $-NR^2S(O)_2CR^2R^{2a}-$, $-CR^2R^{2a}S(O)_2NR^2-$, $-NR^2S(O)_2NR^2-$, $-C(O)NR^2-$, $-NR^2C(O)-$, $-C(O)NR^2CR^2R^{2a}-$, $-NR^2C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)NR^2-$, $-CR^2R^{2a}NR^2C(O)-$, $-NR^2C(O)O-$, $-OC(O)NR^2-$, $-NR^2C(O)NR^2-$, $-NR^2-$, $-NR^2CR^2R^{2a}-$, $-CR^2R^{2a}NR^2-$, O, $-CR^2R^{2a}O-$, and $-OCR^2R^{2a}-$;

Y is selected from:

$(CH_2)_rNR^2R^{2a}$, provided that X-Y do not form a N-N, O-N, or S-N bond,

C_{3-10} carbocyclic residue substituted with 0-2 R^{4a}, and

5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a};

R^4, at each occurrence, is selected from =O, $(CH_2)_rOR^2$, halo, C_{1-4} alkyl, -CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2b}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $CH(=NR^2)NR^2R^{2a}$, $NHC(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, NR^2SO_2-C_{1-4} alkyl, $NR^2SO_2R^5$, $S(O)_pR^5$, $(CF_2)_rCF_3$, $NCH_2R^{1''}$, $OCH_2R^{1''}$, $SCH_2R^{1''}$, $N(CH_2)_2(CH_2)_tR^{1'}$, $O(CH_2)_2(CH_2)_tR^{1'}$, and $S(CH_2)_2(CH_2)_tR^{1'}$,

alternatively, one R^4 is a 5-6 membered aromatic heterocycle containing from 1-4 heteroatoms selected from the group consisting of N, O, and S;

R^{4a}, at each occurrence, is selected from =O, $(CH_2)_rOR^2$, halo, C_{1-4} alkyl, -CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2b}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $CH(=NR^2)NR^2R^{2a}$, $NHC(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, NR^2SO_2-C_{1-4} alkyl, $NR^2SO_2R^5$, $S(O)_pR^5$, and $(CF_2)_rCF_3$;

alternatively, one R^{4a} is a 5-6 membered aromatic heterocycle containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-1 R^5;

R^{4b}, at each occurrence, is selected from =O, $(CH_2)_rOR^3$, halo, C_{1-4} alkyl, -CN, NO_2, $(CH_2)_rNR^3R^{3a}$, $(CH_2)_rC(O)R^3$, $NR^3C(O)R^{3a}$, $C(O)NR^3R^{3a}$, $NR^3C(O)NR^3R^{3a}$, $CH(=NR^3)NR^3R^{3a}$, $NH^3C(=NR^3)NR^3R^{3a}$, $SO_2NR^3R^{3a}$, $NR^3SO_2NR^3R^{3a}$, NR^3SO_2-C_{1-4} alkyl, $NR^3SO_2CF_3$, NR^3SO_2-phenyl, $S(O)_pCF_3$, $S(O)_p$-C_{1-4} alkyl, $S(O)_p$-phenyl, and $(CF_2)_rCF_3$;

R^5, at each occurrence, is selected from CF_3, C_{1-6} alkyl, phenyl substituted with 0-2 R^6, and benzyl substituted with 0-2 R^6;

R^6, at each occurrence, is selected from H, OH, $(CH_2)_rOR^2$, halo, C_{1-4} alkyl, CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2b}$, $NR^2C(O)R^{2b}$, $NR^2C(O)NR^2R^{2a}$, $CH(=NH)NH_2$, $NHC(=NH)NH_2$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, and $NR^2SO_2C_{1-4}$ alkyl;

R^7, at each occurrence, is selected from H, OH, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxy, C_{1-4} alkoxycarbonyl, $(CH_2)_n$-phenyl, C_{6-10} aryloxy, C_{6-10} aryloxycarbonyl, C_{6-10} arylmethylcarbonyl, C_{1-4} alkylcarbonyloxy C_{1-4} alkoxycarbonyl, C_{6-10} arylcarbonyloxy C_{1-4} alkoxycarbonyl, C_{1-6} alkylaminocarbonyl, phenylaminocarbonyl, and phenyl C_{1-4} alkoxycarbonyl;

R^8, at each occurrence, is selected from H, C_{1-6} alkyl and $(CH_2)_n$-phenyl;

alternatively, R^7 and R^8 combine to form a 5 or 6 membered saturated, ring which contains from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

R^9, at each occurrence, is selected from H, C_{1-6} alkyl and $(CH_2)_n$-phenyl;

n, at each occurrence, is selected from 0, 1, 2, and 3;

m, at each occurrence, is selected from 0, 1, and 2;

p, at each occurrence, is selected from 0, 1, and 2;

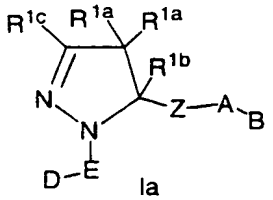
q, at each occurrence is selected from 1 and 2;

r, at each occurrence, is selected from 0, 1, 2, and 3;

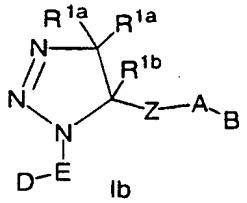
s, at each occurrence, is selected from 0, 1, and 2; and,

t, at each occurrence, is selected from 0 and 1.

[2] In a preferred embodiment, the present invention provides novel compounds of formulae Ia-Ib:



Ia



Ib

wherein;

Z is selected from a CH_2O, OCH_2, CH_2NH, $NHCH_2$, $C(O)$, $CH_2C(O)$, $C(O)CH_2$, $NHC(O)$, $C(O)NH$, $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH, and $NHSO_2$, provided that Z does not form a N-N, N-O, NCH_2N, or NCH_2O bond with group A;

A is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^4;

phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, benzofuranyl, benzothiofuranyl, indolyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, and isoindazolyl;

B is selected from: Y, X-Y, NR^2R^{2a}, $C(=NR^2)NR^2R^{2a}$, and $NR^2C(=NR^2)NR^2R^{2a}$;

X is selected from C_{1-4} alkylene, $-C(O)-$, $-C(=NR)-$, $-CR^2(NR^2R^{2a})-$, $-C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)$, $-C(O)NR^2-$, $-NR^2C(O)-$, $-C(O)NR^2CR^2R^{2a}-$, $-NR^2C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)NR^2-$, $-CR^2R^{2a}NR^2C(O)-$, $-NR^2C(O)NR^2-$, $-NR^2-$, $-NR^2CR^2R^{2a}-$, $-CR^2R^{2a}NR^2-$, O, $-CR^2R^{2a}O-$, and $-OCR^2R^{2a}-$;

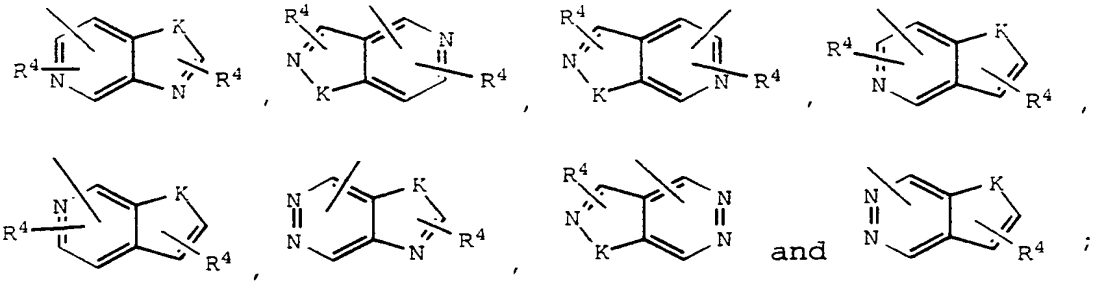
Y is NR^2R^{2a}, provided that X-Y do not form a N-N or O-N bond;

alternatively, Y is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^{4a};

cylcopropyl, cyclopentyl, cyclohexyl, phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, isoxazolinyl, thiazolyl,

isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, benzofuranyl, benzothiofuranyl, indolyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, and isoindazolyl;

alternatively, Y is selected from the following bicyclic heteroaryl ring systems:



and

;

K is selected from O, S, NH, and N.

[3] In a more preferred embodiment, the present invention provides novel compounds of formulae Ia-Ib, wherein;

Z is selected from a C(O), $CH_2C(O)$, $C(O)CH_2$, NHC(O), C(O)NH, $C(O)N(CH_3)$, $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH, and $NHSO_2$, provided that Z does not form a N-N or NCH_2N bond with group A.

[4] In an even more preferred embodiment, the present invention provides novel compounds of formulae Ia-Ib, wherein;

E is phenyl substituted with R or 2-pyridyl substituted with R;

D is selected from $C(O)NH_2$, $C(=NH)NH_2$, CH_2NH_2, CH_2NHCH_3, $CH(CH_3)NH_2$, and $C(CH_3)_2NH_2$; and,

R is selected from H, OCH_3, Cl, and F.

[5] In a further preferred embodiment, the present invention provides novel compounds of formulae Ia-Ib, wherein;

D-E is selected from 3-amidinophenyl, 3-aminomethylphenyl, 3-aminocarbonylphenyl, 3-(methylaminomethyl)phenyl, 3-(1-aminoethyl)phenyl, 3-(2-amino-2-propyl)phenyl, 4-chloro-3-amidinophenyl, 4-chloro-3-aminomethylphenyl, 4-chloro-3-(methylaminomethyl)phenyl, 4-fluoro-3-amidinophenyl, 4-fluoro-3-aminomethylphenyl, 4-fluoro-3-(methylaminomethyl)phenyl, 6-amidinopyrid-2-yl, 6-aminomethylpyrid-2-yl, 6-aminocarbonylpyrid-2-yl, 6-(methylaminomethyl)pyrid-2-yl, 6-(1-aminoethyl)pyrid-2-yl, and 6-(2-amino-2-propyl)pyrid-2-yl.

[6] In another even more preferred embodiment, the present invention provides novel compounds of formulae Ia-Ib, wherein;

Z is $C(O)CH_2$ and CONH, provided that Z does not form a N-N bond with group A;

A is selected from phenyl, pyridyl, and pyrimidyl, and is substituted with 0-2 R^4; and,

B is selected from X-Y, phenyl, pyrrolidino, morpholino, 1,2,3-triazolyl, and imidazolyl, and is substituted with 0-1 R^{4a};

R^4, at each occurrence, is selected from OH, $(CH_2)_rOR^2$, halo, C_{1-4} alkyl, $(CH_2)_rNR^2R^{2a}$, and $(CF_2)_rCF_3$;

R^{4a} is selected from C_{1-4} alkyl, CF_3, $S(O)_pR^5$, $SO_2NR^2R^{2a}$, and 1-CF_3-tetrazol-2-yl;

R^5, at each occurrence, is selected from CF_3, C_{1-6} alkyl, phenyl, and benzyl;

X is CH_2 or C(O); and,

Y is selected from pyrrolidino and morpholino.

[7] In another further preferred embodiment, the present invention provides novel compounds of formulae Ia-Ib, wherein;

A is selected from the group: phenyl, 2-pyridyl, 3-pyridyl, 2-pyrimidyl, 2-Cl-phenyl, 3-Cl-phenyl, 2-F-phenyl, 3-F-phenyl, 2-methylphenyl, 2-aminophenyl, and 2-methoxyphenyl; and,

B is selected from the group: 2-CF_3-phenyl, 2-(aminosulfonyl)phenyl, 2-(methylaminosulfonyl)phenyl, 2-(dimethylaminosulfonyl)phenyl, 1-pyrrolidinocarbonyl, 2-(methylsulfonyl)phenyl, 4-morpholino, 2-(1'-CF_3-tetrazol-2-yl)phenyl, 4-morpholinocarbonyl, 2-methyl-1-imidazolyl, 5-methyl-1-imidazolyl, 2-methylsulfonyl-1-imidazolyl and, 5-methyl-1,2,3-triazolyl.

[8] In another even more preferred embodiment, the present invention provides novel compounds of formulae Ia-Ib, wherein;

E is phenyl substituted with R or 2-pyridyl substituted with R;

D is selected from $C(O)NH_2$, $C(=NH)NH_2$, CH_2NH_2, CH_2NHCH_3, $CH(CH_3)NH_2$, and $C(CH_3)_2NH_2$; and,

R is selected from H, OCH_3, Cl, and F;

Z is $C(O)CH_2$ and CONH, provided that Z does not form a N-N bond with group A;

A is selected from phenyl, pyridyl, and pyrimidyl, and is substituted with 0-2 R^4; and,

B is selected from X-Y, phenyl, pyrrolidino, morpholino, 1,2,3-triazolyl, and imidazolyl, and is substituted with 0-1 R^{4a};

R^4, at each occurrence, is selected from OH, $(CH_2)_rOR^2$, halo, C_{1-4} alkyl, $(CH_2)_rNR^2R^{2a}$, and $(CF_2)_rCF_3$;

R^{4a} is selected from C_{1-4} alkyl, CF_3, $S(O)_pR^5$, $SO_2NR^2R^{2a}$, and 1-CF_3-tetrazol-2-yl;

R^5, at each occurrence, is selected from CF_3, C_{1-6} alkyl, phenyl, and benzyl;

X is CH_2 or C(O); and,

Y is selected from pyrrolidino and morpholino.

[9] In another further preferred embodiment, the present invention provides novel compounds of formulae Ia-Ib, wherein;

D-E is selected from 3-amidinophenyl, 3-aminomethylphenyl, 3-aminocarbonylphenyl, 3-(methylaminomethyl)phenyl, 3-(1-aminoethyl)phenyl, 3-(2-amino-2-propyl)phenyl, 4-chloro-3-amidinophenyl, 4-chloro-3-aminomethylphenyl, 4-chloro-3-(methylaminomethyl)phenyl, 4-fluoro-3-amidinophenyl, 4-fluoro-3-aminomethylphenyl, 4-fluoro-3-(methylaminomethyl)phenyl, 6-amidinopyrid-2-yl, 6-aminomethylpyrid-2-yl, 6-aminocarbonylpyrid-2-yl, 6-(methylaminomethyl)pyrid-2-yl, 6-(1-aminoethyl)pyrid-2-yl, 6-(2-amino-2-propyl)pyrid-2-yl;

A is selected from the group: phenyl, 2-pyridyl, 3-pyridyl, 2-pyrimidyl, 2-Cl-phenyl, 3-Cl-phenyl, 2-F-phenyl, 3-F-phenyl, 2-methylphenyl, 2-aminophenyl, and 2-methoxyphenyl; and,

B is selected from the group: 2-CF_3-phenyl, 2-(aminosulfonyl)phenyl, 2-(methylaminosulfonyl)phenyl, 2-(dimethylaminosulfonyl)phenyl, 1-pyrrolidinocarbonyl, 2-(methylsulfonyl)phenyl, 4-morpholino, 2-(1'-CF_3-tetrazol-2-yl)phenyl, 4-morpholinocarbonyl, 2-methyl-1-imidazolyl, 5-methyl-1-imidazolyl, 2-methylsulfonyl-1-imidazolyl and, 5-methyl-1,2,3-triazolyl.

[10] In a still further preferred embodiment, the present invention provides a novel compound of formula Ia.

[11] In another still further preferred embodiment, the present invention provides a novel compound of formula Ib.

[12] In another even more preferred embodiment, the present invention provides novel compounds of formulae Ia-Ib, wherein;

D is selected from $C(=NR^8)NR^7R^9$, $C(O)NR^7R^8$, NR^7R^8, and $CH_2NR^7R^8$;

E is phenyl substituted with R or pyridyl substituted with R;

R is selected from H, Cl, F, OR^3, CH_3, CH_2CH_3, OCF_3, and CF_3;

Z is selected from C(O), $CH_2C(O)$, $C(O)CH_2$, NHC(O), and C(O)NH, provided that Z does not form a N-N bond with group A;

R^{1a} and R^{1b} are, at each occurrence, independently selected from H, $-(CH_2)_r-R^{1'}$, $NCH_2R^{1''}$, $OCH_2R^{1''}$, $SCH_2R^{1''}$, $N(CH_2)_2(CH_2)_tR^{1'}$, $O(CH_2)_2(CH_2)_tR^{1'}$, and $S(CH_2)_2(CH_2)_tR^{1'}$;

R^{1c} is selected from H, $-(CH_2)_q-R^{1'}$, C_{1-3} alkyl, $C(O)R^{2c}$, $(CF_2)_rCO_2R^{2c}$, and $C(O)NR^2R^{2a}$;

$R^{1'}$, at each occurrence, is selected from H, C_{1-3} alkyl, halo, $(CF_2)_rCF_3$, OR^2, NR^2R^{2a}, $C(O)R^{2c}$, $(CF_2)_rCO_2R^{2c}$, $S(O)_pR^{2b}$, $NR^2(CH_2)_rOR^2$, $NR^2C(O)R^{2b}$, $NR^2C(O)_2R^{2b}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and $NR^2SO_2R^{2b}$;

A is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^4;

phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, and imidazolyl;

B is selected from: Y, X-Y, NR^2R^{2a}, $C(=NR^2)NR^2R^{2a}$, and $NR^2C(=NR^2)NR^2R^{2a}$;

X is selected from CH_2, $-CR^2(CR^2R^{2b})(CH_2)_t-$, $-C(O)-$, $-C(=NR)-$, $-CH(NR^2R^{2a})-$, $-C(O)NR^2-$, $-NR^2C(O)-$, $-NR^2C(O)NR^2-$, $-NR^2-$, and O;

Y is NR^2R^{2a}, provided that X-Y do not form a N-N or O-N bond;

alternatively, Y is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^{4a};

phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, isoxazolinyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl,

1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, and 1,3,4-triazolyl;

R^4, at each occurrence, is selected from =O, OH, Cl, F, C_{1-4} alkyl, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2b}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $CH(=NH)NH_2$, $NHC(=NH)NH_2$, $SO_2NR^2R^{2a}$, NR^2SO_2-C_{1-4} alkyl, $NR^2SO_2R^5$, $S(O)_pR^5$, and $(CF_2)_rCF_3$;

R^{4a}, at each occurrence, is selected from =O, OH, Cl, F, C_{1-4} alkyl, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2b}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $CH(=NH)NH_2$, $NHC(=NH)NH_2$, $SO_2NR^2R^{2a}$, NR^2SO_2-C_{1-4} alkyl, $NR^2SO_2R^5$, $S(O)_pR^5$, $(CF_2)_rCF_3$, and 1-CF_3-tetrazol-2-yl;

R^5, at each occurrence, is selected from CF_3, C_{1-6} alkyl, phenyl substituted with 0-2 R^6, and benzyl substituted with 0-2 R^6;

R^6, at each occurrence, is selected from H, =O, OH, OR^2, Cl, F, CH_3, CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2b}$, $NR^2C(O)R^{2b}$, $CH(=NH)NH_2$, $NHC(=NH)NH_2$, and $SO_2NR^2R^{2a}$;

R^7, at each occurrence, is selected from H, OH, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxy, C_{1-4} alkoxycarbonyl, benzyl, C_{6-10} aryloxy, C_{6-10} aryloxycarbonyl, C_{6-10} arylmethylcarbonyl, C_{1-4} alkylcarbonyloxy C_{1-4} alkoxycarbonyl, C_{6-10} arylcarbonyloxy C_{1-4} alkoxycarbonyl, C_{1-6} alkylaminocarbonyl, phenylaminocarbonyl, and phenyl C_{1-4} alkoxycarbonyl;

R^8, at each occurrence, is selected from H, C_{1-6} alkyl and benzyl; and

alternatively, R^7 and R^8 combine to form a morpholino group; and,

R^9, at each occurrence, is selected from H, C_{1-6} alkyl and benzyl.

[13] In a another further preferred embodiment, the present invention provides novel compounds of formulae Ia-Ib, wherein;

E is phenyl substituted with R or 2-pyridyl substituted with R;

R is selected from H, Cl, F, OCH_3, CH_3, OCF_3, and CF_3;

Z is selected from a $C(O)CH_2$ and C(O)NH, provided that Z does not form a N-N bond with group A;

R^{1a}, at each occurrence, is selected from H, CH_3, CH_2CH_3, Cl, F, CF_3, OCH_3, NR^2R^{2a}, $S(O)_pR^{2b}$, $CH_2S(O)_pR^{2b}$, $CH_2NR^2S(O)_pR^{2b}$, $C(O)R^{2c}$, $CH_2C(O)R^{2c}$, $C(O)NR^2R^{2a}$, and $SO_2NR^2R^{2a}$;

R^{1b} is selected from H, CH_3, CH_2CH_3, Cl, F, CF_3, OCH_3, NR^2R^{2a}, $S(O)_pR^{2b}$, $CH_2S(O)_pR^{2b}$, $CH_2NR^2S(O)_pR^{2b}$, $C(O)R^{2c}$, $CH_2C(O)R^{2c}$, $C(O)NR^2R^{2a}$, and $SO_2NR^2R^{2a}$;

R^{1c} is selected from H, CH_3, CH_2CH_3, CF_3, $CH_2S(O)_pR^{2b}$, $CH_2NR^2S(O)_pR^{2b}$, $C(O)R^{2c}$, $CH_2C(O)R^{2c}$, and $C(O)NR^2R^{2a}$;

A is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^4;

phenyl, pyridyl, pyrimidyl, furanyl, thiophenyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, and imidazolyl;

B is selected from: Y and X-Y;

X is selected from CH_2, $-CR^2(CR^2R^{2b})-$, $-C(O)-$, $-C(=NR)-$, $-CH(NR^2R^{2a})-$, $-C(O)NR^2-$, $-NR^2C(O)-$, $-NR^2C(O)NR^2-$, $-NR^2-$, and O;

Y is NR^2R^{2a}, provided that X-Y do not form a N-N or O-N bond;

alternatively, Y is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^{4a};

phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, isoxazolinyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, and 1,3,4-triazolyl;

R^2, at each occurrence, is selected from H, CF_3, CH_3, benzyl, and phenyl;

R^{2a}, at each occurrence, is selected from H, CF_3, CH_3, benzyl, and phenyl;

R^{2b}, at each occurrence, is selected from CF_3, OCH_3, CH_3, benzyl, and phenyl;

R^{2c}, at each occurrence, is selected from CF_3, OH, OCH_3, CH_3, benzyl, and phenyl;

alternatively, R^2 and R^{2a} combine to form a 5 or 6 membered saturated, partially unsaturated, or unsaturated ring which contains from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

R^3, at each occurrence, is selected from H, CH_3, CH_2CH_3, and phenyl;

R^{3a}, at each occurrence, is selected from H, CH_3, CH_2CH_3, and phenyl;

R^4, at each occurrence, is selected from OH, Cl, F, CH_3, CH_2CH_3, NR^2R^{2a}, $CH_2NR^2R^{2a}$, $C(O)R^{2b}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, and CF_3;

R^{4a}, at each occurrence, is selected from OH, Cl, F, CH_3, CH_2CH_3, NR^2R^{2a}, $CH_2NR^2R^{2a}$, $C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $S(O)_pR^5$, CF_3, and 1-CF_3-tetrazol-2-yl;

R^5, at each occurrence, is selected from CF_3, C_{1-6} alkyl, phenyl substituted with 0-2 R^6, and benzyl substituted with 1 R^6;

R^6, at each occurrence, is selected from H, OH, OCH_3, Cl, F, CH_3, CN, NO_2, NR^2R^{2a}, $CH_2NR^2R^{2a}$, and $SO_2NR^2R^{2a}$;

R^7, at each occurrence, is selected from H, OH, C_{1-3} alkyl, C_{1-3} alkylcarbonyl, C_{1-3} alkoxy, C_{1-4} alkoxycarbonyl, benzyl, phenoxy, phenoxycarbonyl, benzylcarbonyl, C_{1-4} alkylcarbonyloxy C_{1-4} alkoxycarbonyl, phenylcarbonyloxy C_{1-4} alkoxycarbonyl, C_{1-6} alkylaminocarbonyl, phenylaminocarbonyl, and phenyl C_{1-4} alkoxycarbonyl;

R^8, at each occurrence, is selected from H, CH_3, and benzyl; and,

alternatively, R^7 and R^8 combine to form a morpholino group;

R^9, at each occurrence, is selected from H, CH_3, and benzyl.

[14] In a another still further preferred embodiment, the present invention provides novel compounds of formulae Ia-Ib, wherein;

R^{1a}, at each occurrence, is selected from H, CH_3, CH_2CH_3, Cl, F, CF_3, OCH_3, NR^2R^{2a}, $S(O)_pR^{2b}$, $C(O)NR^2R^{2a}$, $CH_2S(O)_pR^{2b}$, $CH_2NR^2S(O)_pR^{2b}$, $C(O)R^{2c}$, $CH_2C(O)R^{2c}$, and $SO_2NR^2R^{2a}$;

R^{1b} is selected from H, CH_3, CH_2CH_3, Cl, F, CF_3, OCH_3, NR^2R^{2a}, $S(O)_pR^{2b}$, $C(O)NR^2R^{2a}$, $CH_2S(O)_pR^{2b}$, $CH_2NR^2S(O)_pR^{2b}$, $C(O)R^{2b}$, $CH_2C(O)R^{2b}$, and $SO_2NR^2R^{2a}$;

R^{1c} is selected from H, CH_3, CH_2CH_3, CF_3, $C(O)NR^2R^{2a}$, $CH_2S(O)_pR^{2b}$, $CH_2NR^2S(O)_pR^{2b}$, $C(O)R^{2b}$, and $CH_2C(O)R^{2b}$;

A is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^4;

phenyl, pyridyl, and pyrimidyl;

B is selected from: Y and X-Y;

X is selected from -C(O)- and O;

Y is NR^2R^{2a}, provided that X-Y do not form a O-N bond;

alternatively, Y is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^{4a};

phenyl, piperazinyl, pyridyl, pyrimidyl, morpholinyl, pyrrolidinyl, imidazolyl, and 1,2,3-triazolyl;

R^2, at each occurrence, is selected from H, CF_3, CH_3, benzyl, and phenyl;

R^{2a}, at each occurrence, is selected from H, CF_3, CH_3, benzyl, and phenyl;

R^{2b}, at each occurrence, is selected from CF_3, OCH_3, CH_3, benzyl, and phenyl;

R^{2c}, at each occurrence, is selected from CF_3, OH, OCH_3, CH_3, benzyl, and phenyl;

alternatively, R^2 and R^{2a} combine to form a ring system selected from pyrrolidinyl, piperazinyl and morpholino;

R^4, at each occurrence, is selected from Cl, F, CH_3, NR^2R^{2a}, and CF_3;

R^{4a}, at each occurrence, is selected from Cl, F, CH_3, $SO_2NR^2R^{2a}$, $S(O)_pR^5$, and CF_3; and,

R^5, at each occurrence, is selected from CF_3 and CH_3.

[15] Specifically preferred compounds of the present invention are selected from the group:

1-(3-amidinophenyl)-5-[[(2'-methylsulfonyl-[1,1']-biphen-4-yl)-aminocarbonyl]-3-trifluoromethyl-pyrazoline; and,

1-(3-aminomethylphenyl)-5-[[(2'-methylsulfonyl-[1,1']-biphen-4-yl)-aminocarbonyl]-3-trifluoromethyl-pyrazoline;

and pharmaceutically acceptable salts thereof.

In a second embodiment, the present invention provides novel pharmaceutical compositions, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt form thereof.

In a third embodiment, the present invention provides a novel method for treating or preventing a thromboembolic disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt form thereof.

DEFINITIONS

The compounds herein described may have asymmetric centers. Compounds of the present invention containing an

asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated.

The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substitent is keto (i.e., =O), then 2 hydrogens on the atom are replaced.

When any variable (e.g., R^6) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R^6, then said group may optionally be substituted with up to two R^6 groups and R^6 at each occurrence is selected independently from the definition of R^6. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein, "C_{1-6} alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, examples of which include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, pentyl, and hexyl; "Alkenyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl, propenyl, and the like.

"Halo" or "halogen" as used herein refers to fluoro, chloro, bromo, and iodo; and "counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, sulfate, and the like.

As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3- to 7-membered monocyclic or bicyclic or 7- to 13-membered bicyclic or tricyclic, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin).

As used herein, the term "heterocycle" or "heterocyclic system" is intended to mean a stable 5- to 7- membered monocyclic or bicyclic or 7- to 10-membered bicyclic heterocyclic ring which is saturated partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. If specifically

noted, a nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. As used herein, the term "aromatic heterocyclic system" is intended to mean a stable 5- to 7-membered monocyclic or bicyclic or 7- to 10-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and from 1 to 4 heterotams independently selected from the group consisting of N, O and S. It is preferred that the total number of S and O atoms in the aromatic heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to, 1H-indazole, 2-pyrrolidonyl, 2H,6H-1,5,2-dithiazinyl, 2H-pyrrolyl, 3H-indolyl, 4-piperidonyl, 4aH-carbazole, 4H-quinolizinyl, 6H-1,2,5-thiadiazinyl, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalonyl, carbazolyl, 4a*H*-carbazolyl, β-carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1*H*-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl., oxazolyl, oxazolidinylperimidinyl, phenanthridinyl, phenanthrolinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, piperidonyl, 4-piperidonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl,

quinoxalinyl, quinuclidinyl, carbolinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, xanthenyl. Preferred heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, indolyl, benzimidazolyl, 1*H*-indazolyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, or isatinoyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic,

sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

"Prodrugs" are intended to include any covalently bonded carriers which release the active parent drug according to formula (I) *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of a compound of formula (I) are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of formula (I) wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug or compound of formula (I) is administered to a mammalian subject, cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of formula (I), and the like. Preferred prodrugs are amidine prodrugs wherein D is $C(=NR^7)NH_2$ or its tautomer $C(=NH)NHR^7$ and R^7 is selected from OH, C_{1-4} alkoxy, C_{6-10} aryloxy, C_{1-4} alkoxycarbonyl, C_{6-10} aryloxycarbonyl, C_{6-10} arylmethylcarbonyl, C_{1-4} alkylcarbonyloxy C_{1-4} alkoxycarbonyl, and C_{6-10} arylcarbonyloxy C_{1-4} alkoxycarbonyl. More preferred prodrugs are where R^7 is

OH, methoxy, ethoxy, benzyloxycarbonyl, methoxycarbonyl, and methylcarbonyloxymethoxycarbonyl.

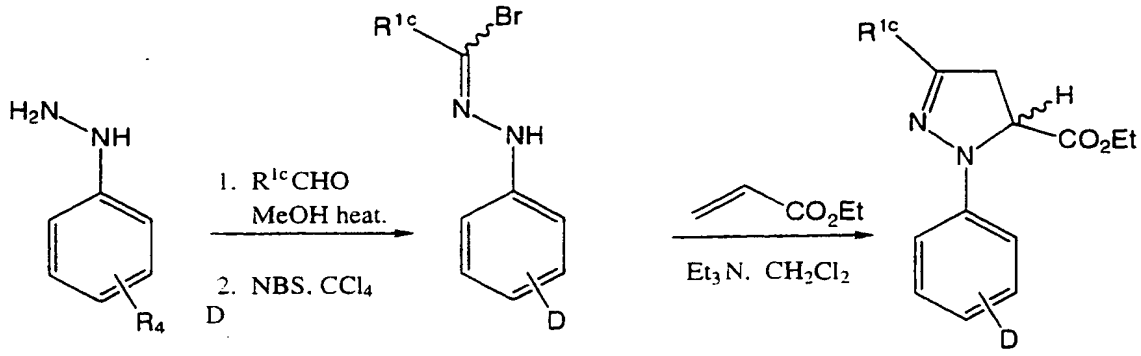
"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

SYNTHESIS

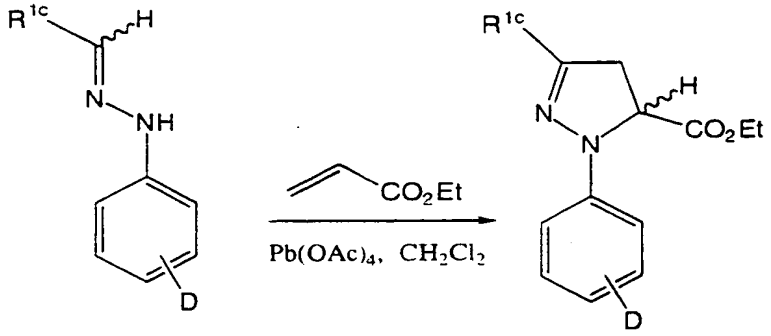
The compounds of the present invention can be prepared in a number of ways known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or by variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. The reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention. It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this invention. An authoritative account describing the many alternatives to the trained practitioner is Greene and Wuts (*Protective Groups In Organic Synthesis*, Wiley and Sons, **1991**). All references cited herein are hereby incorporated in their entirety herein by reference.

Pyrazolines of this invention can be easily prepared via [3+2] cycloaddition of bromo or chloro hydrazone with an appropriate acrylate according to the methodology described by

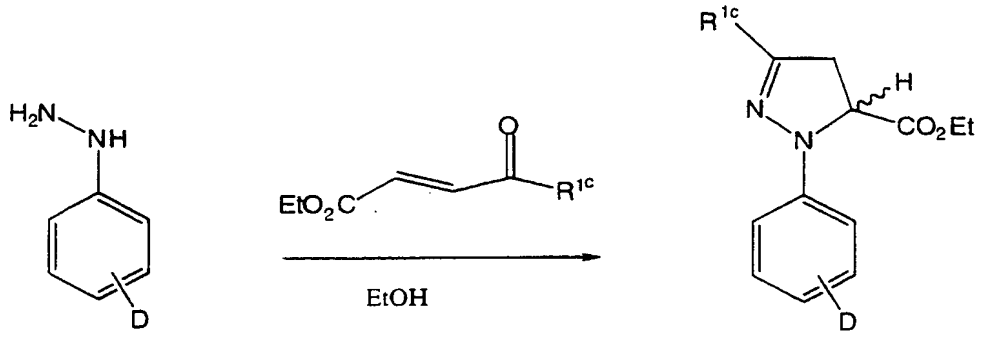
Tewari R. S. and Parihar *Tetrahedron* **1983**, *39*, 129-136, or Krayushkin, M. M. et. al *Izv. Akad. Nauk, Ser. Khim.* **1994**, *1*, 114-117.



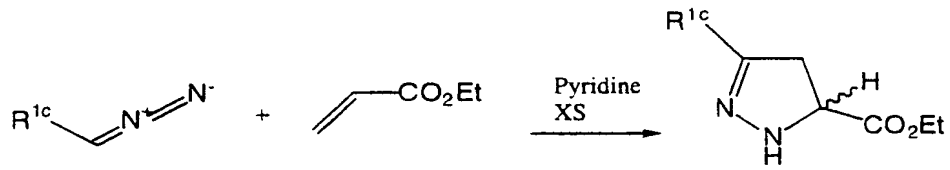
Pyrazoline 5-esters can also be prepared by the treatment of an appropriately substituted hydrazone with lead tetraacetate and an appropriate acrylate in a THF/benzene solvent system according to the procedure of Sasaki T, et. al. *Bull. Chem Soc. Jpn.* **1970**, *43*, 1254.



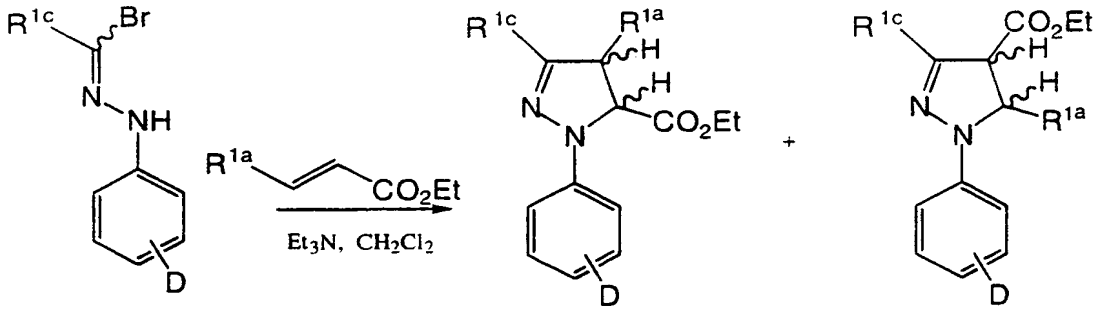
Another method of obtaining pyrazoline 5-esters is the condensation of an appropriate phenyl or heteroaryl hydrazine with an approptiate 2-oxoglutaconate according to Blitzke, T. et. al. *J. Prakt. Chem.* **1993**, *335(8)*, 683.



Alternatively the pyrazoline ester can be prepared by treatment of a diazo-trifluoromethyl derivative with excess acrylate or acrolein in the presence of excess pyridine (Doyle, M. O. et. al. *J. Heterocyclic Chem.* **1983**, *20*, 943).

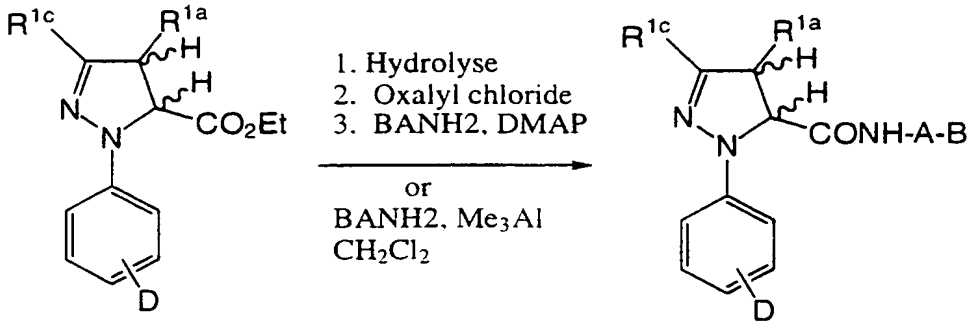


Cycloadditions as described above but with di-substituted olefins should result in the formation of regio-adducts which can be easily separated by standard chromatographic techniques.

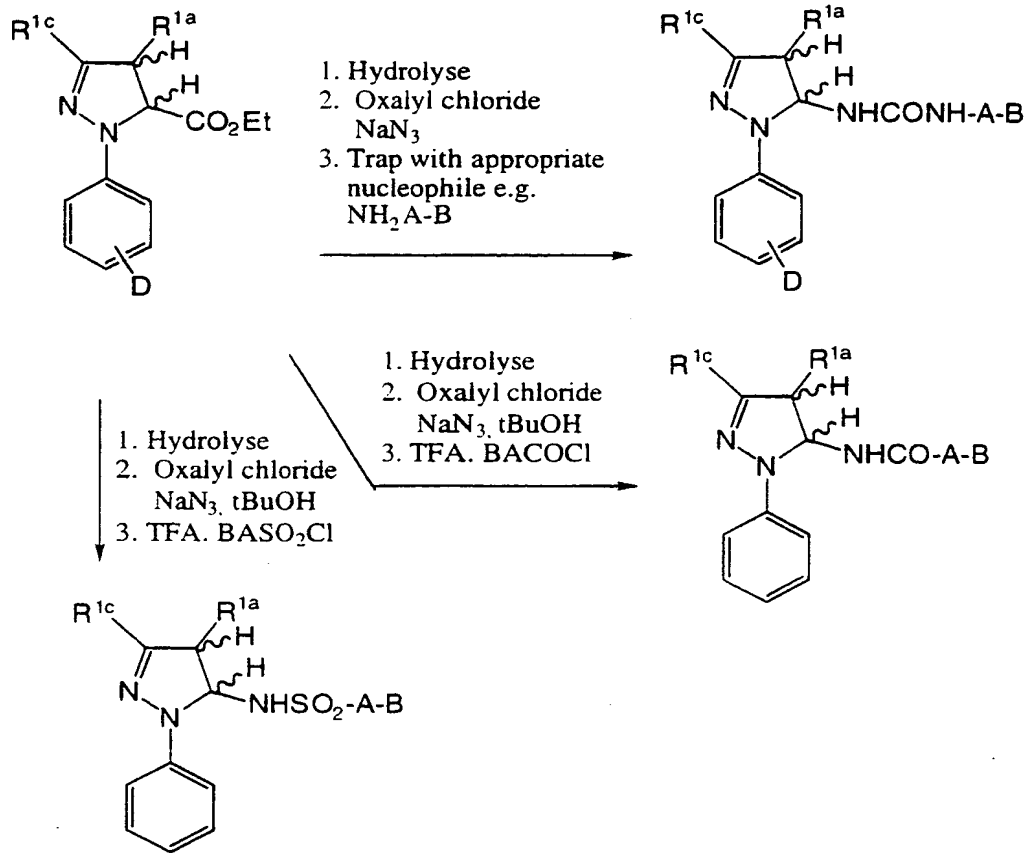


It is understood by those in the art of organic synthesis that such cycloadditions can also be carried out with a wide variety of electron withdrawing olefins with functionalities such as nitro, sulfonyl, sulfonamido, nitrile, phosphate etc. These in turn can be derivatized to appropriate compounds of the present invention.

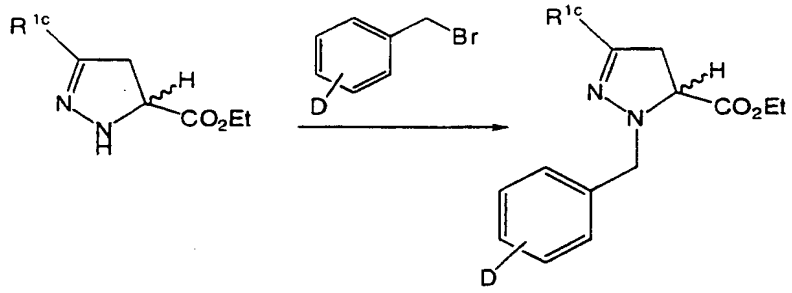
The pyrazoline carboxyesters obtained via any of the above mentioned methodologies can be converted to the amide derivatives via the acid, acid chloride coupling methodlogies or a direct Weinreb (trimethylaluminum, aniline in dichloromethane) coupling technique known to those in the art of organic synthesis. A variety of anilines or amines can be coupled via these methodologies to afford the desired compounds.



Alternatively the ester can be hydrolysed and converted to an amino functionality via the Curtius rearrangement. This in turn can be derivatised to obtain an amido, sulfonamido or urea derivative.



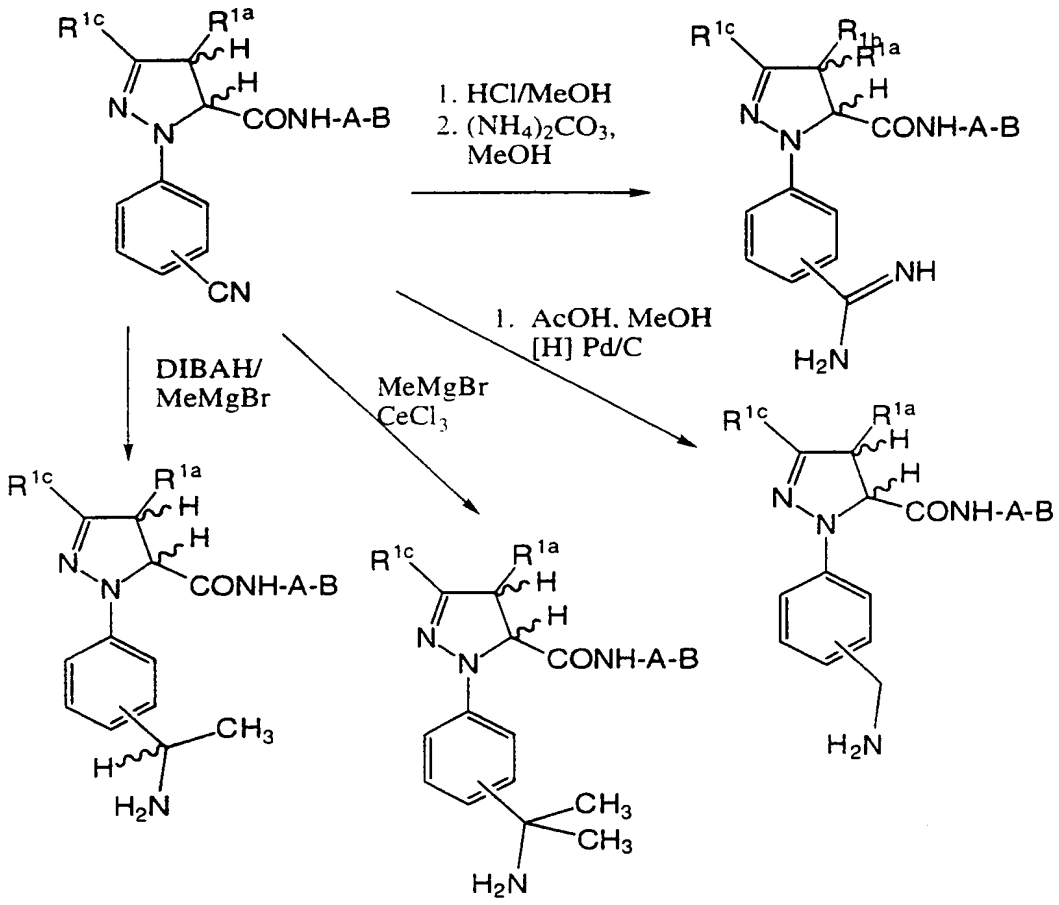
Pyrazolines wherein s is other than 0 can be prepared by alkylation of an appropriate pyrazoline.



The electrophile can consist of simple alkyl halides to heteroaryl alkyl halides. Some of the heteroaryl alkyl groups can include pyridyl, pyrimidyl, imidazolyl etc.

In cases wherein D is a nitrile can be further converted to an amidine functionality via the standard Pinner-amidine reaction sequence known to those in the art or can be

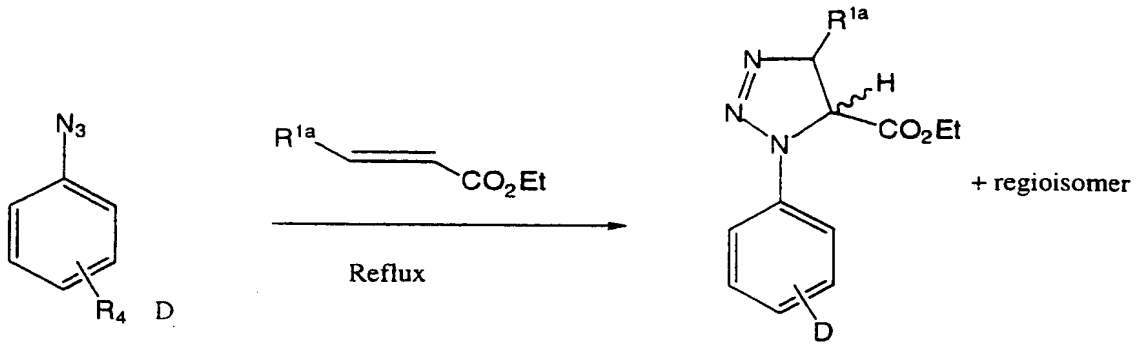
converted to the benzylamine via reduction in an acidic media or can be converted to the secondary and tertiary amine via the DIBAH/MeMgCl or MeMgBr/$CeCl_3$ methodologies outlined below.



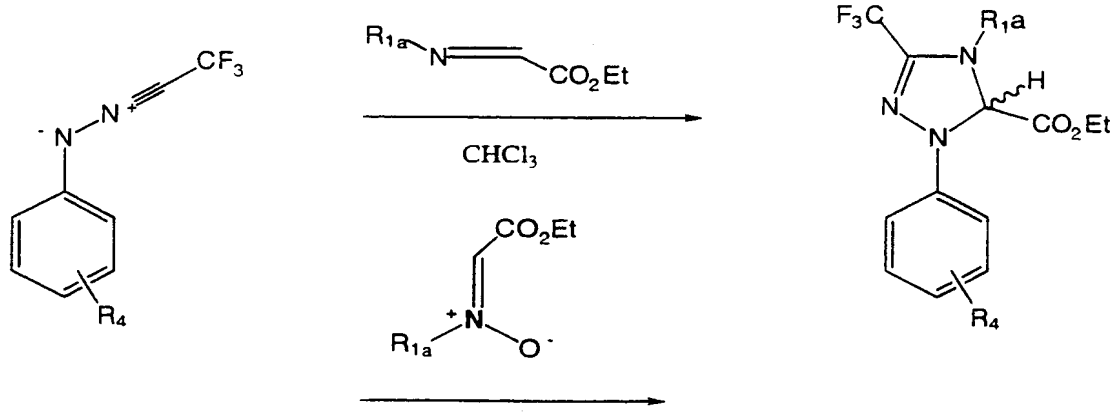
Compounds wherein D is a nitro can be reduced under catalytic Pd/C/MeOH techniques or $SnCl_2$/EtOAc or Zn/AcOH conditions to afford the desired amino derivatives.

Enantiomers of the pyrazolines can be easily obtained either via lipase hydrolysis of its esters or resolution with common chiral bases known to those in the art.

1,2,3-Triazolines can be synthesized via the cycloaddition methodology however in this case the dipole is an aryl azide and the dipolarophile is a variety of olefins bearing an electron withdrawing group such as an ester, amide or sulfonamide.



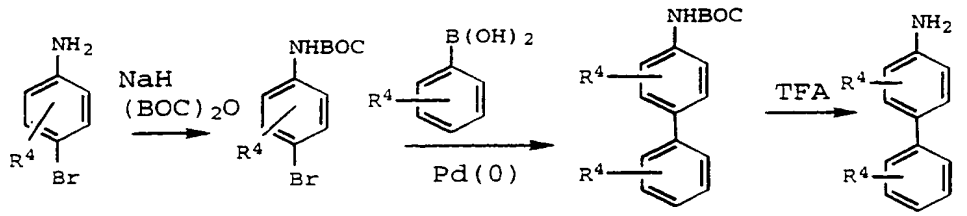
1,2,4-Triazolines can be prepared via the methods of Sandhy J. S. et. al. *Heterocycles* **1985**, *23(5)*, 1143, and *Heterocycles* **1985**, *23(5)*, 1123, by the method described in the scheme below.



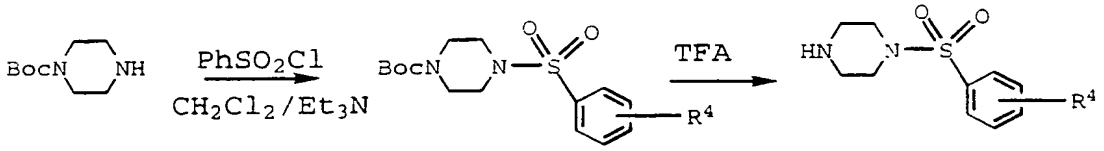
The triazoline esters can then subjected to the standard coupling procedures discussed above to afford the desired amide analogs. These can then further modified to the prepare compounds of the present invention.

Compounds of the present invention wherein AB is a biphenylamine or similar amine may be prepared as shown in the following scheme. 4-Bromoaniline can be protected as Boc-derivative and coupled to a phenylboronic acid under Suzuki conditions (*Bioorg. Med. Chem. Lett.* **1994**, 189). Deprotection with TFA provides the aminobiphenyl compound. Other similar amines wherein A and/or B are heterocycles can be prepared by the same method using appropiately substituted boronic acids and arylbromide. The bromoaniline can also be

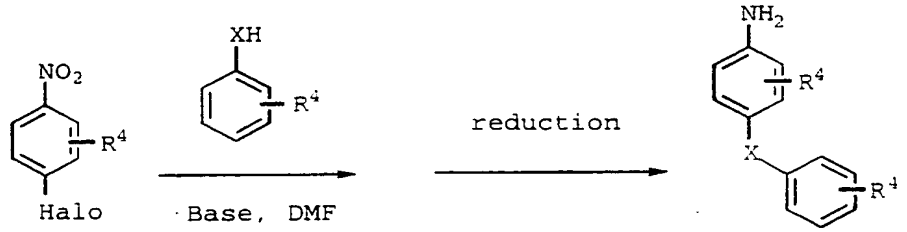
linked to the core ring structures first as described above, and then undergo a Suzuki reaction to give the desired product.



Compounds of the present invention wherein A-B is A-X-Y can be prepared like the piperazine derivative shown below.



The following scheme shows how one can couple cyclic groups wherein X=NH, O, or S.



When B is defined as X-Y, the following description applies. Groups A and B are available either through commercial sources, known in the literature or readily synthesized by the adaptation of standard procedures known to practioners skilled in the art of organic synthesis. The required reactive functional groups appended to analogs of A and B are also available either through commercial sources, known in the literature or readily synthesized by the adaptation of standard procedures known to practioners skilled in the art of organic synthesis. In the tables that follow

the chemistry required to effect the coupling of A to B is outlined.

Table A: Preparation of Amide, Ester, Urea, Sulfonamide and Sulfamide linkages between A and B.

Rxn. No.	if A contains :	then the reactive substituent of Y is :	to give the following product A-X-Y :
1	A-NHR^2 as a substituent	ClC(O)-Y	A-NR^2-C(O)-Y
2	a secondary NH as part of a ring or chain	ClC(O)-Y	A-C(O)-Y
3	A-OH as a substituent	ClC(O)-Y	A-O-C(O)-Y
4	A-NHR^2 as a substituent	ClC(O)-CR^2R^{2a}-Y	A-NR^2-C(O)-CR^2R^{2a}-Y
5	a secondary NH as part of a ring or chain	ClC(O)-CR^2R^{2a}-Y	A-C(O)-CR^2R^{2a}-Y
6	A-OH as a substituent	ClC(O)-CR^2R^{2a}-Y	A-O-C(O)-CR^2R^{2a}-Y
7	A-NHR^3 as a substituent	ClC(O)NR^2-Y	A-NR^2-C(O)NR^2-Y
8	a secondary NH as part of a ring or chain	ClC(O)NR^2-Y	A-C(O)NR^2-Y
9	A-OH as a substituent	ClC(O)NR^2-Y	A-O-C(O)NR^2-Y
10	A-NHR^2 as a substituent	ClSO_2-Y	A-NR^2-SO_2-Y
11	a secondary NH as part of a ring or chain	ClSO_2-Y	A-SO_2-Y
12	A-NHR^2 as a substituent	ClSO_2-CR^2R^{2a}-Y	A-NR^2-SO_2-CR^2R^{2a}-Y

13	a secondary NH as part of a ring or chain	$ClSO_2-CR^2R^{2a}-Y$	$A-SO_2-CR^2R^{2a}-Y$
14	$A-NHR^2$ as a substituent	$ClSO_2-NR^2-Y$	$A-NR^2-SO_2-NR^2-Y$
15	a secondary NH as part of a ring or chain	$ClSO_2-NR^2-Y$	$A-SO_2-NR^2-Y$
16	A-C(O)Cl	HO-Y as a substituent	A-C(O)-O-Y
17	A-C(O)Cl	NHR^2-Y as a substituent	$A-C(O)-NR^2-Y$
18	A-C(O)Cl	a secondary NH as part of a ring or chain	A-C(O)-Y
19	$A-CR^2R^{2a}C(O)Cl$	HO-Y as a substituent	$A-CR^2R^{2a}C(O)-O-Y$
20	$A-CR^2R^{2a}C(O)Cl$	NHR^2-Y as a substituent	$A-CR^2R^{2a}C(O)-NR^2-Y$
21	$A-CR^2R^{2a}C(O)Cl$	a secondary NH as part of a ring or chain	$A-CR^2R^{2a}C(O)-Y$
22	$A-SO_2Cl$	NHR^2-Y as a substituent	$A-SO_2-NR^2-Y$
23	$A-SO_2Cl$	a secondary NH as part of a ring or chain	$A-SO_2-Y$
24	$A-CR^2R^{2a}SO_2Cl$	NHR^2-Y as a substituent	$A-CR^2R^{2a}SO_2-NR^2-Y$
25	$A-CR^2R^{2a}SO_2Cl$	a secondary NH as part of a ring or chain	$A-CR^2R^{2a}SO_2-Y$

The chemistry of Table A can be carried out in aprotic solvents such as a chlorocarbon, pyridine, benzene or toluene, at temperatures ranging from -20°C to the reflux point of the solvent and with or without a trialkylamine base.

Table B: Preparation of ketone linkages between A and B.

Rxn. No.	if A contains :	then the reactive substituent of Y is :	to give the following product A-X-Y :
1	A-C(O)Cl	BrMg-Y	A-C(O)-Y
2	A-CR^2R^{2a}C(O)Cl	BrMg-Y	A-$CR^2R^{2a}{}_2$C(O)-Y
3	A-C(O)Cl	BrMgCR^2R^{2a}-Y	A-C(O)CR^2R^{2a}-Y
4	A-CR^2R^{2a}C(O)Cl	BrMgCR^2R^{2a}-Y	A-CR^2R^{2a}C(O)CR^2R^{2a}-Y

The coupling chemistry of Table B can be carried out by a variety of methods. The Grignard reagent required for Y is prepared from a halogen analog of Y in dry ether, dimethoxyethane or tetrahydrofuran at 0°C to the reflux point of the solvent. This Grignard reagent can be reacted directly under very controlled conditions, that is low temeprature (-20°C or lower) and with a large excess of acid chloride or with catalytic or stoichiometric copper bromide•dimethyl sulfide complex in dimethyl sulfide as a solvent or with a variant thereof. Other methods available include transforming the Grignard reagent to the cadmium reagent and coupling according to the procedure of Carson and Prout (Org. Syn. Col. Vol. 3 (1955) 601) or a coupling mediated by $Fe(acac)_3$ according to Fiandanese et al.(Tetrahedron Lett., (1984) 4805), or a coupling mediated by manganese (II) catalysis (Cahiez and Laboue, Tetrahedron Lett., 33(31), (1992) 4437).

Table C: Preparation of ether and thioether linkages between A and B

Rxn. No.	if A contains :	then the reactive substituent of Y is :	to give the following product A-X-Y :
1	A-OH	Br-Y	A-O-Y
2	A-CR^2R^{2a}-OH	Br-Y	A-CR^2R^{2a}O-Y
3	A-OH	Br-CR^2R^{2a}-Y	A-OCR^2R^{2a}-Y
4	A-SH	Br-Y	A-S-Y
5	A-CR^2R^{2a}-SH	Br-Y	A-CR^2R^{2a}S-Y
6	A-SH	Br-CR^2R^{2a}-Y	A-SCR^2R^{2a}-Y

The ether and thioether linkages of Table C can be prepared by reacting the two components in a polar aprotic solvent such as acetone, dimethylformamide or dimethylsulfoxide in the presence of a base such as potassium carbonate, sodium hydride or potassium t-butoxide at temperature ranging from ambient temperature to the reflux point of the solvent used.

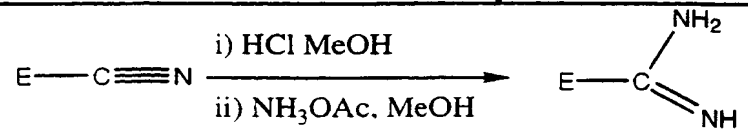
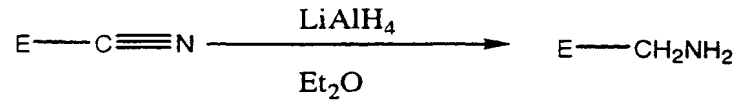
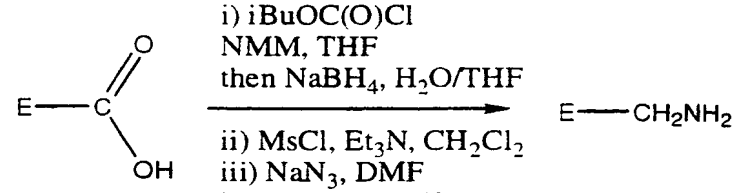
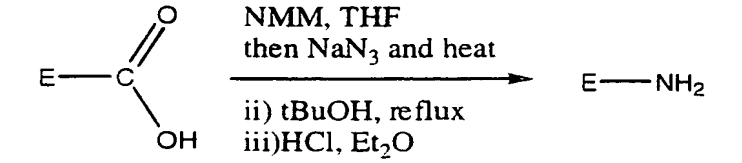
Table D: Preparation of -SO- and -SO2- linkages from thioethers of Table 3.

Rxn. No.	if the starting material is :	and it is oxidized with Alumina (wet)/ Oxone (Greenhalgh, Synlett,(1992) 235) the product is :	and it is oxidized with m-chloroper-benzoic acid (Satoh et al., Chem. Lett. (1992) 381), the product is :
1	A-S-Y	A-S(O)-Y	A-SO_2-Y
2	A-CR^2R^{2a}S-Y	A-CR^2R^{2a}S(O)-Y	A-$CR^2R^{2a}SO_2$-Y
3	A-SCR^2R^{2a}-Y	A-S(O)CR^2R^{2a}-Y	A-$SO_2CR^2R^{2a}$-Y

The thioethers of Table C serve as a convenient starting material for the preparation of the sulfoxide and sulfone analogs of Table D. A combination of wet alumina and oxone can provide a reliable reagent for the oxidation of the

thioether to the sulfoxide while m-chloroperbenzoic acid oxidation will give the sulfone.

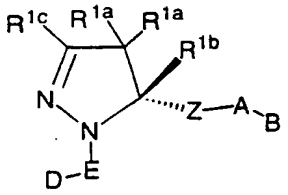
Table E: Methods of Preparing Group E

Rxn	Q	D is to be	then a transformation that may be used is :
1	-CN	-C(=NH)NH2	
2	-CN	-CH2NH2	
3	-CO2H	-CH2NH2	
4	-CO2H	-NH2	

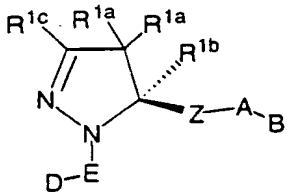
In Table E several methods of transforming a functional group Q into group D of Formula 1 are shown. While not all possible functional groups for Q and D are listed and the synthetic methods suggested are not comprehensive, Table E is meant to illustrate strategies and transformations available to a practitioner skilled in the art of organic synthesis for preparing compounds of Formula 1. In reaction 1 of Table E the transformation of a nitrile into an amidine by the Pinner methodology is shown; in reaction 2 the direct reduction of a nitrile by a hydride reducing agent to a methylene amine is illustrated. In reaction 3, the utility of a carboxylic acid, which may be readily derived from its ester or a nitrile if necessary, in the preparation of a methylene amine is shown. This synthetic route is exceptionally flexible because of the

several stable intermediates prepared *en route* to the final product. As outlined, formation of an activated analog, such as the mixed anhydride, allows for the mild reduction of the acid to the methylene alcohol, this may in turn be transformed into a leaving group by sulfonylation or halogenation or protected with a suitable protecting group to be transformed later in the synthesis as the chemistry demands. Once the methylene alcohol is so activated, displacement by an efficient nitrogen nucleophile, such as azide anion, can again provide another suitably stable analog, -the methylene azide- which may be used as a protected form of the methylene amine or transformed directly into the methylene amine group by reduction. Reaction 4 addresses the problem of appending the amine functionality directly through a bond to group E of Formula 1. Once again, the carboxylic acid provides a convenient *entre* into this selection for group D. The well-know Curtius rearrangement is illustrated here; an activated acid analog can be used to form an acyl azide which upon thermal decomposition is rearranged to the corresponding isocyanate. The isocyanate intermediate may then be captured as a stable carbamate by the addition of a suitable alcohol and further heating. This carbamate can be used as a stable protecting group for the amine or cleaved directly to the desired D. Alternatively, it may be convenient to quench the isocyanate intermediate with water to give the amine directly.

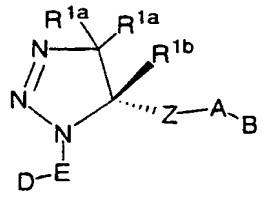
One diastereomer of a compound of Formula I may display superior activity compared with the others. Thus, the following stereochemistries are considered to be a part of the present invention.



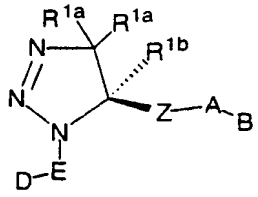
Ia_1



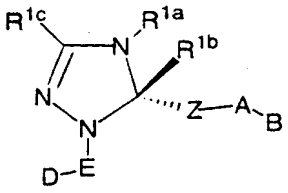
Ia_2



Ib_1



Ib_2



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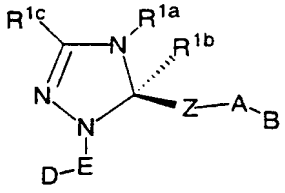
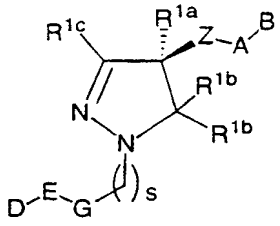
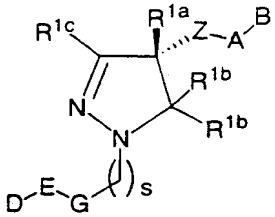


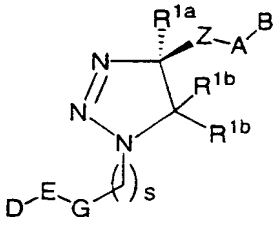
Ic_2



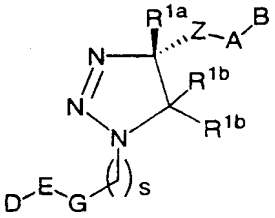
IIa_1



IIa_2



IIb_1



IIb_2

When required, separation of the racemic material can be achieved by HPLC using a chiral column or by a resolution using a resolving agent such as camphonic chloride as in Steven D. Young, et al, *Antimicrobial Agents and Chemotheraphy*, **1995**, 2602-2605. A chiral compound of Formula I may also be directly synthesized using a chiral catalyst or a chiral ligand, e.g., Andrew S. Thompson, et al, *Tet. lett.* **1995**, *36*, 8937-8940).

Other features of the invention will become apparent in the course of the following descriptions of exemplary

embodiments which are given for illustration of the invention and are not intended to be limiting thereof.

EXAMPLES

Examples 1 and 2

1-(3-Amidinophenyl)-5-[[(2'-methylsulfonyl-[1,1']-biphen-4-yl)-aminocarbonyl]-3-trifluoromethyl-pyrazoline and 1-(3-aminomethylphenyl)-5-[[(2'-methylsulfonyl-[1,1']-biphen-4-yl)-aminocarbonyl]-3-trifluoromethyl-pyrazoline

Part A: To a methanolic solution containing meta-cyanophenyl-hydrazine (2 g, 15.03 mmol) was added trifluoromethylacetaldehyde hydrate (1.74 g, 15.03 mmol). The reaction mixture was heated to gentle reflux overnight. Methanol was stripped off to afford yellow crystals of pure hydrazone (2.99g, 93%). ^{1}HNMR ($CDCl_3$)δ: 10.10 (bs, 1H), 7.33 (m, 2H), 7.10 (m, 2H) ppm; ESI (-ve) mass spectrum analysis m/z (relative intensity) 212 (M-H, 100).

Part B: NCS (1.02 g, 7.69 mmol) was added to a DMF (25 mL) solution of the compound prepared in part A (1.64 g, 7.69 mmol). The reaction mixture was stirred at room temperature over night, quenched with water (500 mL) and organics extracted with ethyl acetate (2x100 mL) dried ($MgSO_4$) and evaporated to a reddish brown oil. The oil was redissolved in chloroform (25 mL) and to this solution was added ethyl acrylate (10 mL) followed by slow addition of triethylamine (0.81 mL, 5.75 mmoL). The reaction mixture was refluxed for 18h cooled and quenched with dil. hydrochloric acid (1N, 20 mL). The organic layer was separated and evaporated to an oil. Chromatography on silica gel (7:3, Hexane:ethylacetate) afforded a colorless oil which solidified on standing (1.5 g, 62%). ^{1}HNMR($CDCl_3$)δ: 7.40-7.22 (m, 4H), 4.89 (dd, J = 6.2 and 13.4Hz, 1H), 4.24 (q, 2H), 3.63-3.50 (dd, J = 1.9 and 13.2Hz, 1H), 3.38 (dd, J = 1.9 and 14Hz, 1H), 1.23 (t, 3H) ppm; ESI mass spectrum analysis m/z (relative intensity) 312 (M+H, 100).

Part C: The product from part B was treated with 2'-methylsulfonyl-4-amino-[1,1']biphenyl under Weinreb conditions (trimethylaluminum in dichloromethane) to afford pure coupled product (oil) after silica gel column chromatography (hexane:ethyl acetate 7:3). ^{1}HNMR($CDCl_3$)δ: 8.40 (bs, 1H), 8.17 (dd, J = 1.1 and 7.8Hz, 1H), 7.65-7.25 (m, 11H), 4.90 (m, 1H), 3.78 (m, 1H), 3.38 (dd, J = 1.5 and 8.1Hz, 1H), 2.69 s, 3H); ESI (-ve) mass spectrum analysis m/z (rel. intensity) 511 (M-H, 100).

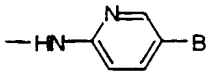
Part D: The product from part C was subjected to the Pinner amidine reaction sequence (HCl/MeOH followed by ammonium carbonate in methanol), purified via standard HPLC purification, lyophilization to afford (40% yield) of Example 1 as colorless crystals. ^{1}HNMR($DMSO_6$)δ: 9.36 (bs, 1.5H), 9.00 (bs, 1.5Hz), 8.06 (d, J = 7.7Hz, 1H), 7.53-7.78 (m, 6H), 7.35 (d, J = 8.1Hz, 3H), 7.27 (d, J = 8.0Hz, 1H), 7.17 (d, J = 8.5Hz, 1H), 5.33 (dd, J = 6.2 and 13.2Hz, 1H), 3.76 (t, 1H), 3.40 (d, J = 3.1Hz, 1H), 2.84(s, 3H) ppm; ESI (+ve) mass spectum analysis m/z (relative intensity) 530 (M+H, 100).

Additionally, the compound form Part C was subjected to reduction using 10% Pd/C in an acidic medium (methanol/acetic acid). Purification via standard HPLC techniques and lyophilization afforded the benzylamine (10% yield). ^{1}HNMR($DMSO_6$)δ: 8.07 (bs, 2H), 8.01 (d, J = 8Hz, 1H), 7.70 (m, 1H), 7.59 (m, 3H), 7.28 (m, 4H), 6.95 (d, J = 8Hz, 1H), 6.83 (dd, J = 1/5 and 8Hz, 1H), 6.40 (bs, 2H), 5.22 (dd, J = 6.5 and 13Hz, 1H), 4.00 (m, 1H), 3.71 (m, 1H), 3.34 (dd, J = 1.5 and 8Hz, 1H), 2.84 (s, 3H) ppm; ESI mass spectrum analysis m/z (relative intensity) 517 (M+H, 100).

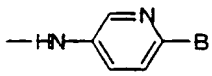
The following tables contain representative examples of the present invention. Each entry in each table is intended to be paired with each formulae at the start of the table. For example, in Table 1, example 1 is intended to be paired

with each of formulae a-ttt and in Table 2, example 1 is intended to be paired with each of formulae a-ss.

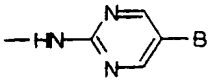
The following groups are intended for group A in the following tables.



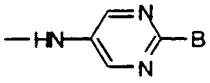
2-pyridyl



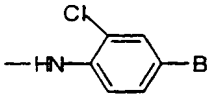
3-pyridyl



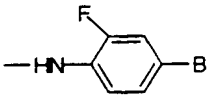
2-pyrimidyl



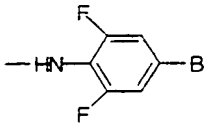
5-pyrimidyl



2-Cl-phenyl

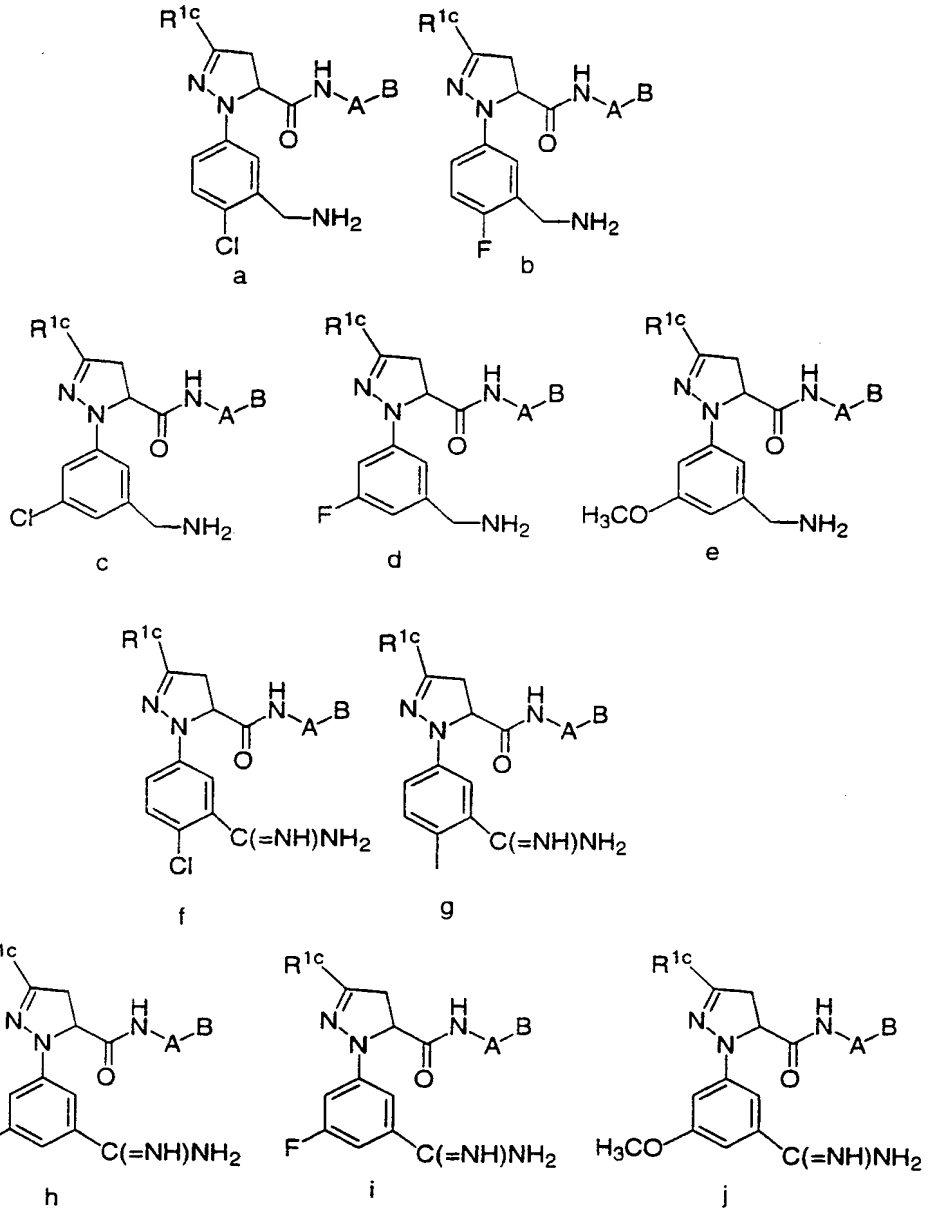


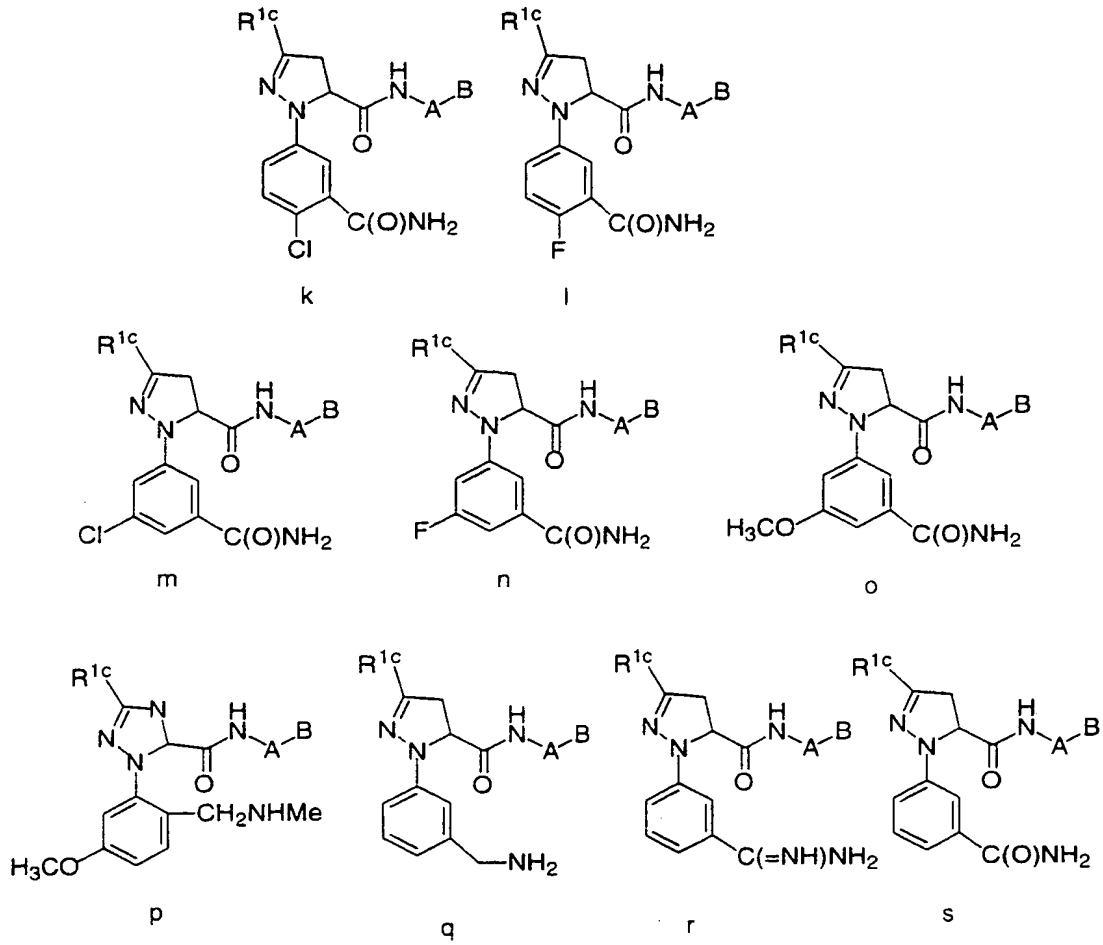
2-F-phenyl



2,6-diF-phenyl

Table 1





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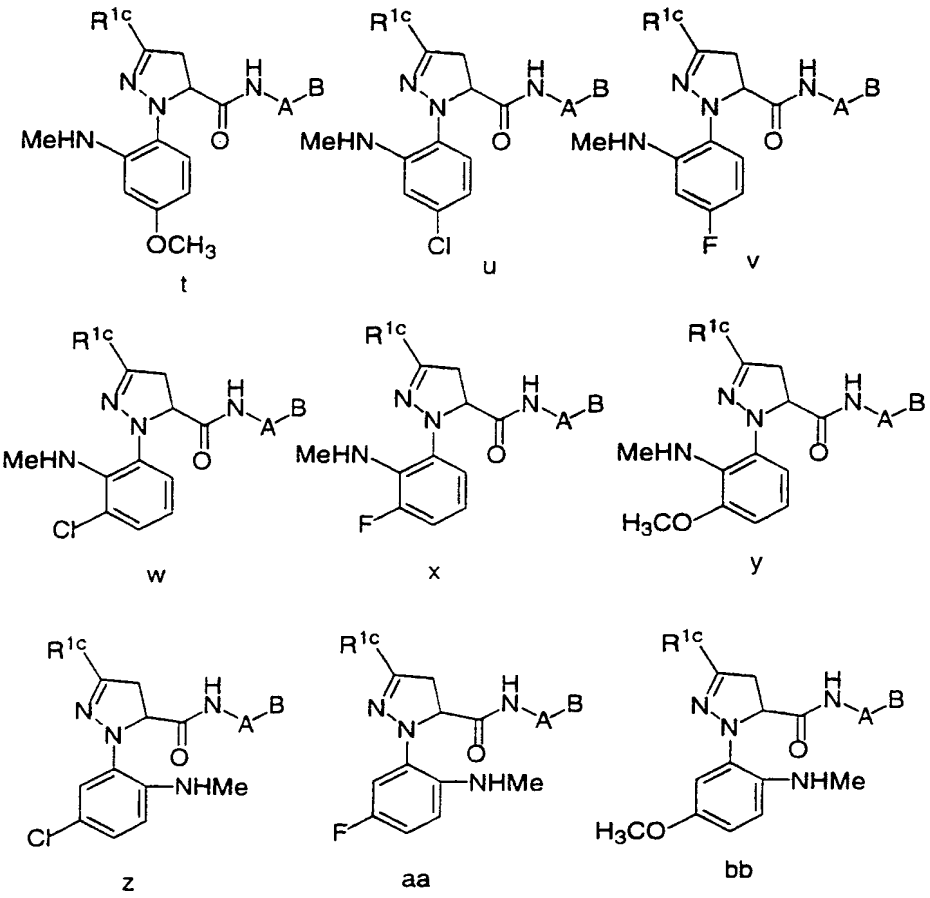

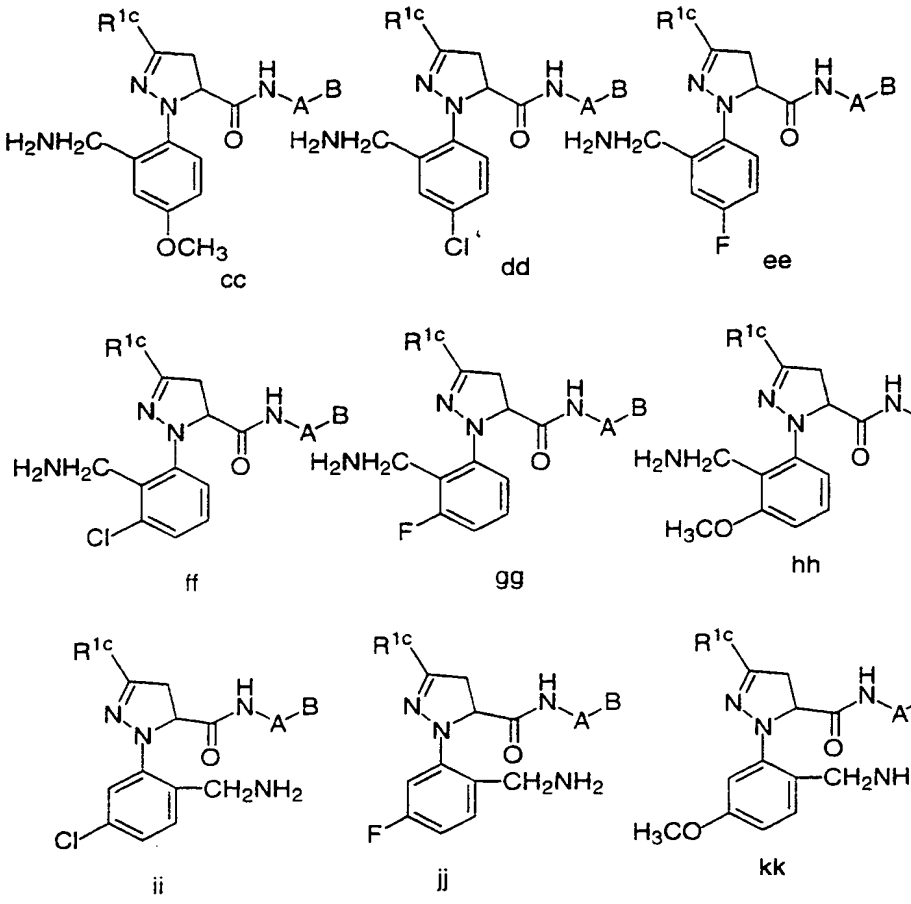

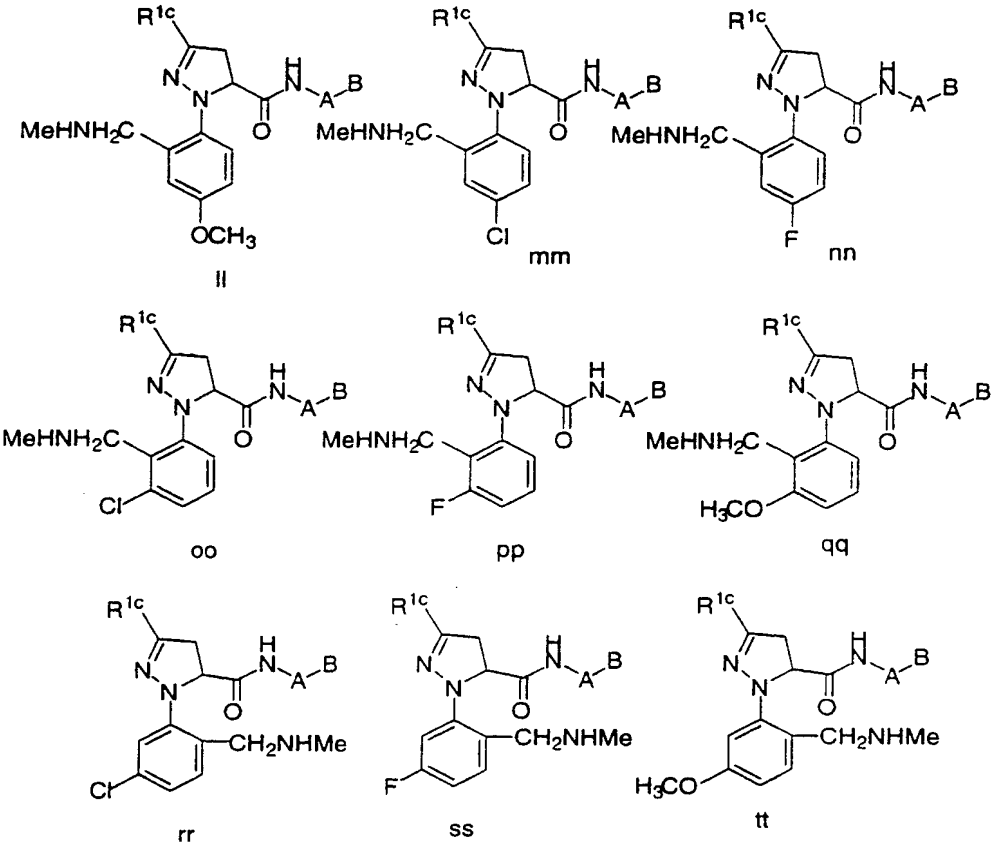

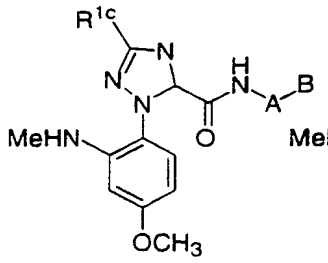

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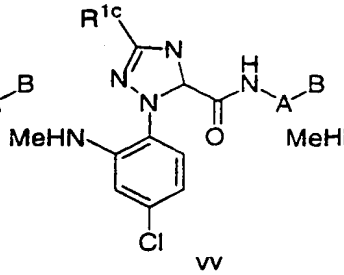

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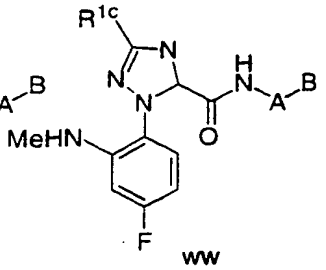

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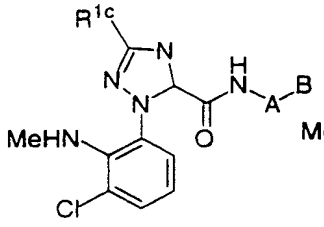

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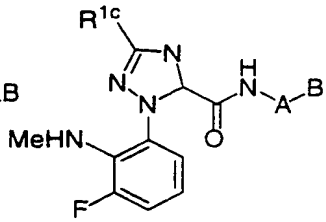

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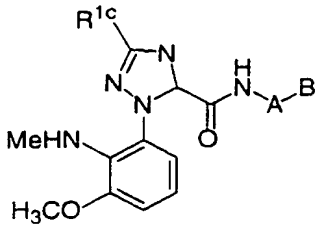

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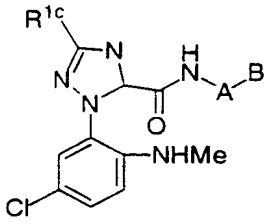

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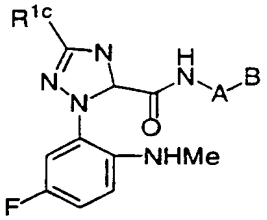

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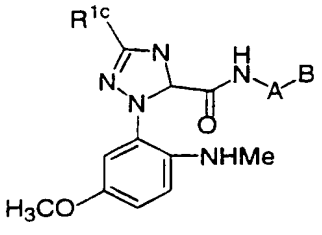

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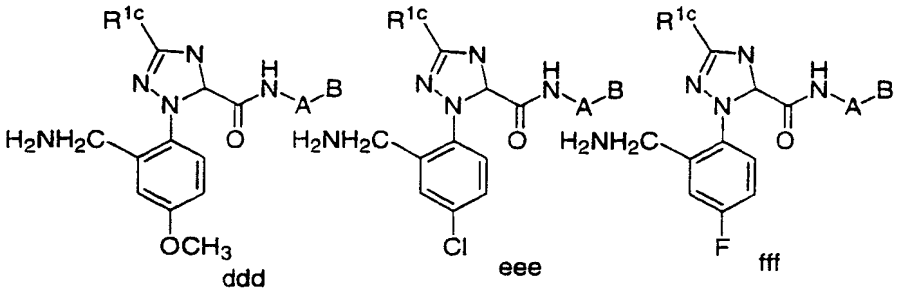

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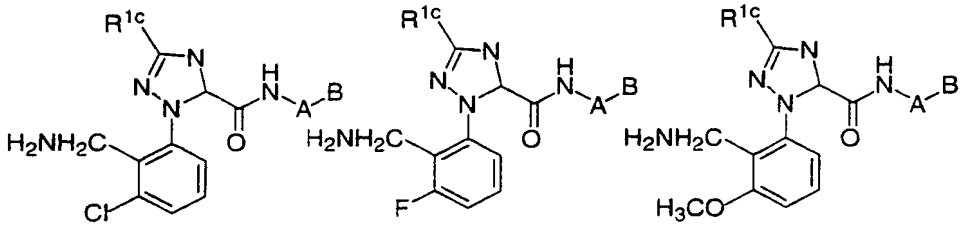

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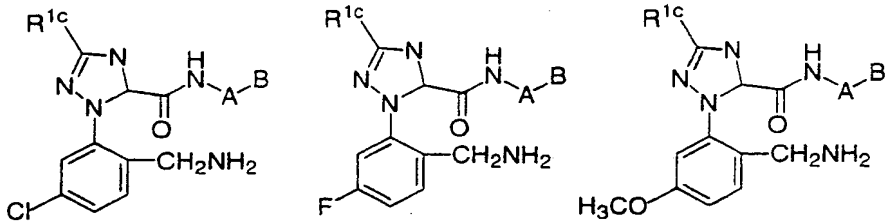

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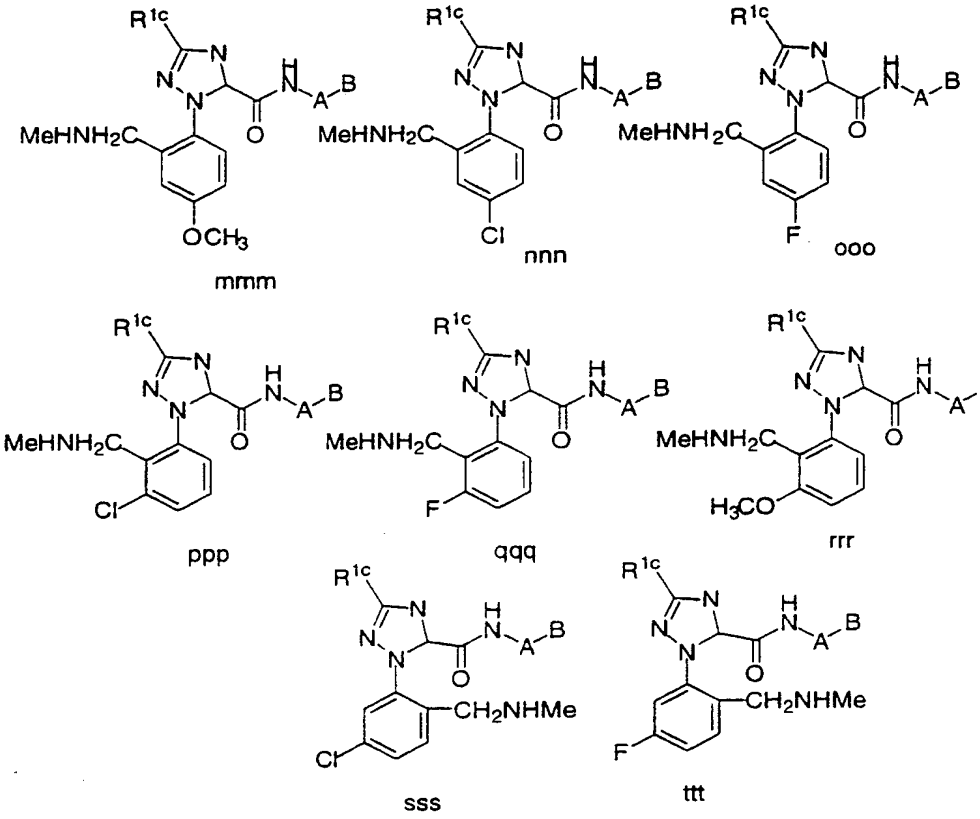

Ex #	R^{1c}	A	B
1	CH_3	phenyl	2-(aminosulfonyl)phenyl
2	CH_3	phenyl	2-(methylaminosulfonyl)phenyl
3	CH_3	phenyl	1-pyrrolidinocarbonyl
4	CH_3	phenyl	2-(methylsulfonyl)phenyl
5	CH_3	phenyl	4-morpholino
6	CH_3	phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
7	CH_3	phenyl	4-morpholinocarbonyl
8	CH_3	phenyl	2-methyl-1-imidazolyl
9	CH_3	phenyl	5-methyl-1-imidazolyl
10	CH_3	phenyl	2-methylsulfonyl-1-imidazolyl
11	CH_3	2-pyridyl	2-(aminosulfonyl)phenyl
12	CH_3	2-pyridyl	2-(methylaminosulfonyl)phenyl
13	CH_3	2-pyridyl	1-pyrrolidinocarbonyl
14	CH_3	2-pyridyl	2-(methylsulfonyl)phenyl
15	CH_3	2-pyridyl	4-morpholino
16	CH_3	2-pyridyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
17	CH_3	2-pyridyl	4-morpholinocarbonyl

18	CH_3	2-pyridyl	2-methyl-1-imidazolyl
19	CH_3	2-pyridyl	5-methyl-1-imidazolyl
20	CH_3	2-pyridyl	2-methylsulfonyl-1-imidazolyl
21	CH_3	3-pyridyl	2-(aminosulfonyl)phenyl
22	CH_3	3-pyridyl	2-(methylaminosulfonyl)phenyl
23	CH_3	3-pyridyl	1-pyrrolidinocarbonyl
24	CH_3	3-pyridyl	2-(methylsulfonyl)phenyl
25	CH_3	3-pyridyl	4-morpholino
26	CH_3	3-pyridyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
27	CH_3	3-pyridyl	4-morpholinocarbonyl
28	CH_3	3-pyridyl	2-methyl-1-imidazolyl
29	CH_3	3-pyridyl	5-methyl-1-imidazolyl
30	CH_3	3-pyridyl	2-methylsulfonyl-1-imidazolyl
31	CH_3	2-pyrimidyl	2-(aminosulfonyl)phenyl
32	CH_3	2-pyrimidyl	2-(methylaminosulfonyl)phenyl
33	CH_3	2-pyrimidyl	1-pyrrolidinocarbonyl
34	CH_3	2-pyrimidyl	2-(methylsulfonyl)phenyl
35	CH_3	2-pyrimidyl	4-morpholino
36	CH_3	2-pyrimidyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
37	CH_3	2-pyrimidyl	4-morpholinocarbonyl
38	CH_3	2-pyrimidyl	2-methyl-1-imidazolyl
39	CH_3	2-pyrimidyl	5-methyl-1-imidazolyl
40	CH_3	2-pyrimidyl	2-methylsulfonyl-1-imidazolyl
41	CH_3	5-pyrimidyl	2-(aminosulfonyl)phenyl
42	CH_3	5-pyrimidyl	2-(methylaminosulfonyl)phenyl
43	CH_3	5-pyrimidyl	1-pyrrolidinocarbonyl
44	CH_3	5-pyrimidyl	2-(methylsulfonyl)phenyl
45	CH_3	5-pyrimidyl	4-morpholino
46	CH_3	5-pyrimidyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
47	CH_3	5-pyrimidyl	4-morpholinocarbonyl
48	CH_3	5-pyrimidyl	2-methyl-1-imidazolyl
49	CH_3	5-pyrimidyl	5-methyl-1-imidazolyl
50	CH_3	5-pyrimidyl	2-methylsulfonyl-1-imidazolyl
51	CH_3	2-Cl-phenyl	2-(aminosulfonyl)phenyl
52	CH_3	2-Cl-phenyl	2-(methylaminosulfonyl)phenyl
53	CH_3	2-Cl-phenyl	1-pyrrolidinocarbonyl
54	CH_3	2-Cl-phenyl	2-(methylsulfonyl)phenyl

55	CH_3	2-Cl-phenyl	4-morpholino
56	CH_3	2-Cl-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
57	CH_3	2-Cl-phenyl	4-morpholinocarbonyl
58	CH_3	2-Cl-phenyl	2-methyl-1-imidazolyl
59	CH_3	2-Cl-phenyl	5-methyl-1-imidazolyl
60	CH_3	2-Cl-phenyl	2-methylsulfonyl-1-imidazolyl
61	CH_3	2-F-phenyl	2-(aminosulfonyl)phenyl
62	CH_3	2-F-phenyl	2-(methylaminosulfonyl)phenyl
63	CH_3	2-F-phenyl	1-pyrrolidinocarbonyl
64	CH_3	2-F-phenyl	2-(methylsulfonyl)phenyl
65	CH_3	2-F-phenyl	4-morpholino
66	CH_3	2-F-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
67	CH_3	2-F-phenyl	4-morpholinocarbonyl
68	CH_3	2-F-phenyl	2-methyl-1-imidazolyl
69	CH_3	2-F-phenyl	5-methyl-1-imidazolyl
70	CH_3	2-F-phenyl	2-methylsulfonyl-1-imidazolyl
71	CH_3	2,6-diF-phenyl	2-(aminosulfonyl)phenyl
72	CH_3	2,6-diF-phenyl	2-(methylaminosulfonyl)phenyl
73	CH_3	2,6-diF-phenyl	1-pyrrolidinocarbonyl
74	CH_3	2,6-diF-phenyl	2-(methylsulfonyl)phenyl
75	CH_3	2,6-diF-phenyl	4-morpholino
76	CH_3	2,6-diF-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
77	CH_3	2,6-diF-phenyl	4-morpholinocarbonyl
78	CH_3	2,6-diF-phenyl	2-methyl-1-imidazolyl
79	CH_3	2,6-diF-phenyl	5-methyl-1-imidazolyl
80	CH_3	2,6-diF-phenyl	2-methylsulfonyl-1-imidazolyl
81	CH_2CH_3	phenyl	2-(aminosulfonyl)phenyl
82	CH_2CH_3	phenyl	2-(methylaminosulfonyl)phenyl
83	CH_2CH_3	phenyl	1-pyrrolidinocarbonyl
84	CH_2CH_3	phenyl	2-(methylsulfonyl)phenyl
85	CH_2CH_3	phenyl	4-morpholino
86	CH_2CH_3	phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
87	CH_2CH_3	phenyl	4-morpholinocarbonyl
88	CH_2CH_3	phenyl	2-methyl-1-imidazolyl
89	CH_2CH_3	phenyl	5-methyl-1-imidazolyl
90	CH_2CH_3	phenyl	2-methylsulfonyl-1-imidazolyl
91	CH_2CH_3	2-pyridyl	2-(aminosulfonyl)phenyl

92	CH_2CH_3	2-pyridyl	2-(methylaminosulfonyl)phenyl
93	CH_2CH_3	2-pyridyl	1-pyrrolidinocarbonyl
94	CH_2CH_3	2-pyridyl	2-(methylsulfonyl)phenyl
95	CH_2CH_3	2-pyridyl	4-morpholino
96	CH_2CH_3	2-pyridyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
97	CH_2CH_3	2-pyridyl	4-morpholinocarbonyl
98	CH_2CH_3	2-pyridyl	2-methyl-1-imidazolyl
99	CH_2CH_3	2-pyridyl	5-methyl-1-imidazolyl
100	CH_2CH_3	2-pyridyl	2-methylsulfonyl-1-imidazolyl
101	CH_2CH_3	3-pyridyl	2-(aminosulfonyl)phenyl
102	CH_2CH_3	3-pyridyl	2-(methylaminosulfonyl)phenyl
103	CH_2CH_3	3-pyridyl	1-pyrrolidinocarbonyl
104	CH_2CH_3	3-pyridyl	2-(methylsulfonyl)phenyl
105	CH_2CH_3	3-pyridyl	4-morpholino
106	CH_2CH_3	3-pyridyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
107	CH_2CH_3	3-pyridyl	4-morpholinocarbonyl
108	CH_2CH_3	3-pyridyl	2-methyl-1-imidazolyl
109	CH_2CH_3	3-pyridyl	5-methyl-1-imidazolyl
110	CH_2CH_3	3-pyridyl	2-methylsulfonyl-1-imidazolyl
111	CH_2CH_3	2-pyrimidyl	2-(aminosulfonyl)phenyl
112	CH_2CH_3	2-pyrimidyl	2-(methylaminosulfonyl)phenyl
113	CH_2CH_3	2-pyrimidyl	1-pyrrolidinocarbonyl
114	CH_2CH_3	2-pyrimidyl	2-(methylsulfonyl)phenyl
115	CH_2CH_3	2-pyrimidyl	4-morpholino
116	CH_2CH_3	2-pyrimidyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
117	CH_2CH_3	2-pyrimidyl	4-morpholinocarbonyl
118	CH_2CH_3	2-pyrimidyl	2-methyl-1-imidazolyl
119	CH_2CH_3	2-pyrimidyl	5-methyl-1-imidazolyl
120	CH_2CH_3	2-pyrimidyl	2-methylsulfonyl-1-imidazolyl
121	CH_2CH_3	5-pyrimidyl	2-(aminosulfonyl)phenyl
122	CH_2CH_3	5-pyrimidyl	2-(methylaminosulfonyl)phenyl
123	CH_2CH_3	5-pyrimidyl	1-pyrrolidinocarbonyl
124	CH_2CH_3	5-pyrimidyl	2-(methylsulfonyl)phenyl
125	CH_2CH_3	5-pyrimidyl	4-morpholino
126	CH_2CH_3	5-pyrimidyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
127	CH_2CH_3	5-pyrimidyl	4-morpholinocarbonyl
128	CH_2CH_3	5-pyrimidyl	2-methyl-1-imidazolyl

129	CH_2CH_3	5-pyrimidyl	5-methyl-1-imidazolyl
130	CH_2CH_3	5-pyrimidyl	2-methylsulfonyl-1-imidazolyl
131	CH_2CH_3	2-Cl-phenyl	2-(aminosulfonyl)phenyl
132	CH_2CH_3	2-Cl-phenyl	2-(methylaminosulfonyl)phenyl
133	CH_2CH_3	2-Cl-phenyl	1-pyrrolidinocarbonyl
134	CH_2CH_3	2-Cl-phenyl	2-(methylsulfonyl)phenyl
135	CH_2CH_3	2-Cl-phenyl	4-morpholino
136	CH_2CH_3	2-Cl-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
137	CH_2CH_3	2-Cl-phenyl	4-morpholinocarbonyl
138	CH_2CH_3	2-Cl-phenyl	2-methyl-1-imidazolyl
139	CH_2CH_3	2-Cl-phenyl	5-methyl-1-imidazolyl
140	CH_2CH_3	2-Cl-phenyl	2-methylsulfonyl-1-imidazolyl
141	CH_2CH_3	2-F-phenyl	2-(aminosulfonyl)phenyl
142	CH_2CH_3	2-F-phenyl	2-(methylaminosulfonyl)phenyl
143	CH_2CH_3	2-F-phenyl	1-pyrrolidinocarbonyl
144	CH_2CH_3	2-F-phenyl	2-(methylsulfonyl)phenyl
145	CH_2CH_3	2-F-phenyl	4-morpholino
146	CH_2CH_3	2-F-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
147	CH_2CH_3	2-F-phenyl	4-morpholinocarbonyl
148	CH_2CH_3	2-F-phenyl	2-methyl-1-imidazolyl
149	CH_2CH_3	2-F-phenyl	5-methyl-1-imidazolyl
150	CH_2CH_3	2-F-phenyl	2-methylsulfonyl-1-imidazolyl
151	CH_2CH_3	2,6-diF-phenyl	2-(aminosulfonyl)phenyl
152	CH_2CH_3	2,6-diF-phenyl	2-(methylaminosulfonyl)phenyl
153	CH_2CH_3	2,6-diF-phenyl	1-pyrrolidinocarbonyl
154	CH_2CH_3	2,6-diF-phenyl	2-(methylsulfonyl)phenyl
155	CH_2CH_3	2,6-diF-phenyl	4-morpholino
156	CH_2CH_3	2,6-diF-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
157	CH_2CH_3	2,6-diF-phenyl	4-morpholinocarbonyl
158	CH_2CH_3	2,6-diF-phenyl	2-methyl-1-imidazolyl
159	CH_2CH_3	2,6-diF-phenyl	5-methyl-1-imidazolyl
160	CH_2CH_3	2,6-diF-phenyl	2-methylsulfonyl-1-imidazolyl
161	CF_3	phenyl	2-(aminosulfonyl)phenyl
162	CF_3	phenyl	2-(methylaminosulfonyl)phenyl
163	CF_3	phenyl	1-pyrrolidinocarbonyl
164	CF_3	phenyl	2-(methylsulfonyl)phenyl
165	CF_3	phenyl	4-morpholino

166	CF_3	phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
167	CF_3	phenyl	4-morpholinocarbonyl
168	CF_3	phenyl	2-methyl-1-imidazolyl
169	CF_3	phenyl	5-methyl-1-imidazolyl
170	CF_3	phenyl	2-methylsulfonyl-1-imidazolyl
171	CF_3	2-pyridyl	2-(aminosulfonyl)phenyl
172	CF_3	2-pyridyl	2-(methylaminosulfonyl)phenyl
173	CF_3	2-pyridyl	1-pyrrolidinocarbonyl
174	CF_3	2-pyridyl	2-(methylsulfonyl)phenyl
175	CF_3	2-pyridyl	4-morpholino
176	CF_3	2-pyridyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
177	CF_3	2-pyridyl	4-morpholinocarbonyl
178	CF_3	2-pyridyl	2-methyl-1-imidazolyl
179	CF_3	2-pyridyl	5-methyl-1-imidazolyl
180	CF_3	2-pyridyl	2-methylsulfonyl-1-imidazolyl
181	CF_3	3-pyridyl	2-(aminosulfonyl)phenyl
182	CF_3	3-pyridyl	2-(methylaminosulfonyl)phenyl
183	CF_3	3-pyridyl	1-pyrrolidinocarbonyl
184	CF_3	3-pyridyl	2-(methylsulfonyl)phenyl
185	CF_3	3-pyridyl	4-morpholino
186	CF_3	3-pyridyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
187	CF_3	3-pyridyl	4-morpholinocarbonyl
188	CF_3	3-pyridyl	2-methyl-1-imidazolyl
189	CF_3	3-pyridyl	5-methyl-1-imidazolyl
190	CF_3	3-pyridyl	2-methylsulfonyl-1-imidazolyl
191	CF_3	2-pyrimidyl	2-(aminosulfonyl)phenyl
192	CF_3	2-pyrimidyl	2-(methylaminosulfonyl)phenyl
193	CF_3	2-pyrimidyl	1-pyrrolidinocarbonyl
194	CF_3	2-pyrimidyl	2-(methylsulfonyl)phenyl
195	CF_3	2-pyrimidyl	4-morpholino
196	CF_3	2-pyrimidyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
197	CF_3	2-pyrimidyl	4-morpholinocarbonyl
198	CF_3	2-pyrimidyl	2-methyl-1-imidazolyl
199	CF_3	2-pyrimidyl	5-methyl-1-imidazolyl
200	CF_3	2-pyrimidyl	2-methylsulfonyl-1-imidazolyl
201	CF_3	5-pyrimidyl	2-(aminosulfonyl)phenyl
202	CF_3	5-pyrimidyl	2-(methylaminosulfonyl)phenyl

203	CF_3	5-pyrimidyl	1-pyrrolidinocarbonyl
204	CF_3	5-pyrimidyl	2-(methylsulfonyl)phenyl
205	CF_3	5-pyrimidyl	4-morpholino
206	CF_3	5-pyrimidyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
207	CF_3	5-pyrimidyl	4-morpholinocarbonyl
208	CF_3	5-pyrimidyl	2-methyl-1-imidazolyl
209	CF_3	5-pyrimidyl	5-methyl-1-imidazolyl
210	CF_3	5-pyrimidyl	2-methylsulfonyl-1-imidazolyl
211	CF_3	2-Cl-phenyl	2-(aminosulfonyl)phenyl
212	CF_3	2-Cl-phenyl	2-(methylaminosulfonyl)phenyl
213	CF_3	2-Cl-phenyl	1-pyrrolidinocarbonyl
214	CF_3	2-Cl-phenyl	2-(methylsulfonyl)phenyl
215	CF_3	2-Cl-phenyl	4-morpholino
216	CF_3	2-Cl-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
217	CF_3	2-Cl-phenyl	4-morpholinocarbonyl
218	CF_3	2-Cl-phenyl	2-methyl-1-imidazolyl
219	CF_3	2-Cl-phenyl	5-methyl-1-imidazolyl
220	CF_3	2-Cl-phenyl	2-methylsulfonyl-1-imidazolyl
221	CF_3	2-F-phenyl	2-(aminosulfonyl)phenyl
222	CF_3	2-F-phenyl	2-(methylaminosulfonyl)phenyl
223	CF_3	2-F-phenyl	1-pyrrolidinocarbonyl
224	CF_3	2-F-phenyl	2-(methylsulfonyl)phenyl
225	CF_3	2-F-phenyl	4-morpholino
226	CF_3	2-F-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
227	CF_3	2-F-phenyl	4-morpholinocarbonyl
228	CF_3	2-F-phenyl	2-methyl-1-imidazolyl
229	CF_3	2-F-phenyl	5-methyl-1-imidazolyl
230	CF_3	2-F-phenyl	2-methylsulfonyl-1-imidazolyl
231	CF_3	2,6-diF-phenyl	2-(aminosulfonyl)phenyl
232	CF_3	2,6-diF-phenyl	2-(methylaminosulfonyl)phenyl
233	CF_3	2,6-diF-phenyl	1-pyrrolidinocarbonyl
234	CF_3	2,6-diF-phenyl	2-(methylsulfonyl)phenyl
235	CF_3	2,6-diF-phenyl	4-morpholino
236	CF_3	2,6-diF-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
237	CF_3	2,6-diF-phenyl	4-morpholinocarbonyl
238	CF_3	2,6-diF-phenyl	2-methyl-1-imidazolyl
239	CF_3	2,6-diF-phenyl	5-methyl-1-imidazolyl

240	CF_3	2,6-diF-phenyl	2-methylsulfonyl-1-imidazolyl
241	SCH_3	phenyl	2-(aminosulfonyl)phenyl
242	SCH_3	phenyl	2-(methylaminosulfonyl)phenyl
243	SCH_3	phenyl	1-pyrrolidinocarbonyl
244	SCH_3	phenyl	2-(methylsulfonyl)phenyl
245	SCH_3	phenyl	4-morpholino
246	SCH_3	phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
247	SCH_3	phenyl	4-morpholinocarbonyl
248	SCH_3	phenyl	2-methyl-1-imidazolyl
249	SCH_3	phenyl	5-methyl-1-imidazolyl
250	SCH_3	phenyl	2-methylsulfonyl-1-imidazolyl
251	SCH_3	2-pyridyl	2-(aminosulfonyl)phenyl
252	SCH_3	2-pyridyl	2-(methylaminosulfonyl)phenyl
253	SCH_3	2-pyridyl	1-pyrrolidinocarbonyl
254	SCH_3	2-pyridyl	2-(methylsulfonyl)phenyl
255	SCH_3	2-pyridyl	4-morpholino
256	SCH_3	2-pyridyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
257	SCH_3	2-pyridyl	4-morpholinocarbonyl
258	SCH_3	2-pyridyl	2-methyl-1-imidazolyl
259	SCH_3	2-pyridyl	5-methyl-1-imidazolyl
260	SCH_3	2-pyridyl	2-methylsulfonyl-1-imidazolyl
261	SCH_3	3-pyridyl	2-(aminosulfonyl)phenyl
262	SCH_3	3-pyridyl	2-(methylaminosulfonyl)phenyl
263	SCH_3	3-pyridyl	1-pyrrolidinocarbonyl
264	SCH_3	3-pyridyl	2-(methylsulfonyl)phenyl
265	SCH_3	3-pyridyl	4-morpholino
266	SCH_3	3-pyridyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
267	SCH_3	3-pyridyl	4-morpholinocarbonyl
268	SCH_3	3-pyridyl	2-methyl-1-imidazolyl
269	SCH_3	3-pyridyl	5-methyl-1-imidazolyl
270	SCH_3	3-pyridyl	2-methylsulfonyl-1-imidazolyl
271	SCH_3	2-pyrimidyl	2-(aminosulfonyl)phenyl
272	SCH_3	2-pyrimidyl	2-(methylaminosulfonyl)phenyl
273	SCH_3	2-pyrimidyl	1-pyrrolidinocarbonyl
274	SCH_3	2-pyrimidyl	2-(methylsulfonyl)phenyl
275	SCH_3	2-pyrimidyl	4-morpholino
276	SCH_3	2-pyrimidyl	2-(1'-CF_3-tetrazol-2-yl)phenyl

277	SCH_3	2-pyrimidyl	4-morpholinocarbonyl
278	SCH_3	2-pyrimidyl	2-methyl-1-imidazolyl
279	SCH_3	2-pyrimidyl	5-methyl-1-imidazolyl
280	SCH_3	2-pyrimidyl	2-methylsulfonyl-1-imidazolyl
281	SCH_3	5-pyrimidyl	2-(aminosulfonyl)phenyl
282	SCH_3	5-pyrimidyl	2-(methylaminosulfonyl)phenyl
283	SCH_3	5-pyrimidyl	1-pyrrolidinocarbonyl
284	SCH_3	5-pyrimidyl	2-(methylsulfonyl)phenyl
285	SCH_3	5-pyrimidyl	4-morpholino
286	SCH_3	5-pyrimidyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
287	SCH_3	5-pyrimidyl	4-morpholinocarbonyl
288	SCH_3	5-pyrimidyl	2-methyl-1-imidazolyl
289	SCH_3	5-pyrimidyl	5-methyl-1-imidazolyl
290	SCH_3	5-pyrimidyl	2-methylsulfonyl-1-imidazolyl
291	SCH_3	2-Cl-phenyl	2-(aminosulfonyl)phenyl
292	SCH_3	2-Cl-phenyl	2-(methylaminosulfonyl)phenyl
293	SCH_3	2-Cl-phenyl	1-pyrrolidinocarbonyl
294	SCH_3	2-Cl-phenyl	2-(methylsulfonyl)phenyl
295	SCH_3	2-Cl-phenyl	4-morpholino
296	SCH_3	2-Cl-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
297	SCH_3	2-Cl-phenyl	4-morpholinocarbonyl
298	SCH_3	2-Cl-phenyl	2-methyl-1-imidazolyl
299	SCH_3	2-Cl-phenyl	5-methyl-1-imidazolyl
300	SCH_3	2-Cl-phenyl	2-methylsulfonyl-1-imidazolyl
301	SCH_3	2-F-phenyl	2-(aminosulfonyl)phenyl
302	SCH_3	2-F-phenyl	2-(methylaminosulfonyl)phenyl
303	SCH_3	2-F-phenyl	1-pyrrolidinocarbonyl
304	SCH_3	2-F-phenyl	2-(methylsulfonyl)phenyl
305	SCH_3	2-F-phenyl	4-morpholino
306	SCH_3	2-F-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
307	SCH_3	2-F-phenyl	4-morpholinocarbonyl
308	SCH_3	2-F-phenyl	2-methyl-1-imidazolyl
309	SCH_3	2-F-phenyl	5-methyl-1-imidazolyl
310	SCH_3	2-F-phenyl	2-methylsulfonyl-1-imidazolyl
311	SCH_3	2,6-diF-phenyl	2-(aminosulfonyl)phenyl
312	SCH_3	2,6-diF-phenyl	2-(methylaminosulfonyl)phenyl
313	SCH_3	2,6-diF-phenyl	1-pyrrolidinocarbonyl

314	SCH_3	2,6-diF-phenyl	2-(methylsulfonyl)phenyl
315	SCH_3	2,6-diF-phenyl	4-morpholino
316	SCH_3	2,6-diF-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
317	SCH_3	2,6-diF-phenyl	4-morpholinocarbonyl
318	SCH_3	2,6-diF-phenyl	2-methyl-1-imidazolyl
319	SCH_3	2,6-diF-phenyl	5-methyl-1-imidazolyl
320	SCH_3	2,6-diF-phenyl	2-methylsulfonyl-1-imidazolyl
321	$SOCH_3$	phenyl	2-(aminosulfonyl)phenyl
322	$SOCH_3$	phenyl	2-(methylaminosulfonyl)phenyl
323	$SOCH_3$	phenyl	1-pyrrolidinocarbonyl
324	$SOCH_3$	phenyl	2-(methylsulfonyl)phenyl
325	$SOCH_3$	phenyl	4-morpholino
326	$SOCH_3$	phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
327	$SOCH_3$	phenyl	4-morpholinocarbonyl
328	$SOCH_3$	phenyl	2-methyl-1-imidazolyl
329	$SOCH_3$	phenyl	5-methyl-1-imidazolyl
330	$SOCH_3$	phenyl	2-methylsulfonyl-1-imidazolyl
331	$SOCH_3$	2-pyridyl	2-(aminosulfonyl)phenyl
332	$SOCH_3$	2-pyridyl	2-(methylaminosulfonyl)phenyl
333	$SOCH_3$	2-pyridyl	1-pyrrolidinocarbonyl
334	$SOCH_3$	2-pyridyl	2-(methylsulfonyl)phenyl
335	$SOCH_3$	2-pyridyl	4-morpholino
336	$SOCH_3$	2-pyridyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
337	$SOCH_3$	2-pyridyl	4-morpholinocarbonyl
338	$SOCH_3$	2-pyridyl	2-methyl-1-imidazolyl
339	$SOCH_3$	2-pyridyl	5-methyl-1-imidazolyl
340	$SOCH_3$	2-pyridyl	2-methylsulfonyl-1-imidazolyl
341	$SOCH_3$	3-pyridyl	2-(aminosulfonyl)phenyl
342	$SOCH_3$	3-pyridyl	2-(methylaminosulfonyl)phenyl
343	$SOCH_3$	3-pyridyl	1-pyrrolidinocarbonyl
344	$SOCH_3$	3-pyridyl	2-(methylsulfonyl)phenyl
345	$SOCH_3$	3-pyridyl	4-morpholino
346	$SOCH_3$	3-pyridyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
347	$SOCH_3$	3-pyridyl	4-morpholinocarbonyl
348	$SOCH_3$	3-pyridyl	2-methyl-1-imidazolyl
349	$SOCH_3$	3-pyridyl	5-methyl-1-imidazolyl
350	$SOCH_3$	3-pyridyl	2-methylsulfonyl-1-imidazolyl

351	$SOCH_3$	2-pyrimidyl	2-(aminosulfonyl)phenyl
352	$SOCH_3$	2-pyrimidyl	2-(methylaminosulfonyl)phenyl
353	$SOCH_3$	2-pyrimidyl	1-pyrrolidinocarbonyl
354	$SOCH_3$	2-pyrimidyl	2-(methylsulfonyl)phenyl
355	$SOCH_3$	2-pyrimidyl	4-morpholino
356	$SOCH_3$	2-pyrimidyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
357	$SOCH_3$	2-pyrimidyl	4-morpholinocarbonyl
358	$SOCH_3$	2-pyrimidyl	2-methyl-1-imidazolyl
359	$SOCH_3$	2-pyrimidyl	5-methyl-1-imidazolyl
360	$SOCH_3$	2-pyrimidyl	2-methylsulfonyl-1-imidazolyl
361	$SOCH_3$	5-pyrimidyl	2-(aminosulfonyl)phenyl
362	$SOCH_3$	5-pyrimidyl	2-(methylaminosulfonyl)phenyl
363	$SOCH_3$	5-pyrimidyl	1-pyrrolidinocarbonyl
364	$SOCH_3$	5-pyrimidyl	2-(methylsulfonyl)phenyl
365	$SOCH_3$	5-pyrimidyl	4-morpholino
366	$SOCH_3$	5-pyrimidyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
367	$SOCH_3$	5-pyrimidyl	4-morpholinocarbonyl
368	$SOCH_3$	5-pyrimidyl	2-methyl-1-imidazolyl
369	$SOCH_3$	5-pyrimidyl	5-methyl-1-imidazolyl
370	$SOCH_3$	5-pyrimidyl	2-methylsulfonyl-1-imidazolyl
371	$SOCH_3$	2-Cl-phenyl	2-(aminosulfonyl)phenyl
372	$SOCH_3$	2-Cl-phenyl	2-(methylaminosulfonyl)phenyl
373	$SOCH_3$	2-Cl-phenyl	1-pyrrolidinocarbonyl
374	$SOCH_3$	2-Cl-phenyl	2-(methylsulfonyl)phenyl
375	$SOCH_3$	2-Cl-phenyl	4-morpholino
376	$SOCH_3$	2-Cl-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
377	$SOCH_3$	2-Cl-phenyl	4-morpholinocarbonyl
378	$SOCH_3$	2-Cl-phenyl	2-methyl-1-imidazolyl
379	$SOCH_3$	2-Cl-phenyl	5-methyl-1-imidazolyl
380	$SOCH_3$	2-Cl-phenyl	2-methylsulfonyl-1-imidazolyl
381	$SOCH_3$	2-F-phenyl	2-(aminosulfonyl)phenyl
382	$SOCH_3$	2-F-phenyl	2-(methylaminosulfonyl)phenyl
383	$SOCH_3$	2-F-phenyl	1-pyrrolidinocarbonyl
384	$SOCH_3$	2-F-phenyl	2-(methylsulfonyl)phenyl
385	$SOCH_3$	2-F-phenyl	4-morpholino
386	$SOCH_3$	2-F-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
387	$SOCH_3$	2-F-phenyl	4-morpholinocarbonyl

388	$SOCH_3$	2-F-phenyl	2-methyl-1-imidazolyl
389	$SOCH_3$	2-F-phenyl	5-methyl-1-imidazolyl
390	$SOCH_3$	2-F-phenyl	2-methylsulfonyl-1-imidazolyl
391	$SOCH_3$	2,6-diF-phenyl	2-(aminosulfonyl)phenyl
392	$SOCH_3$	2,6-diF-phenyl	2-(methylaminosulfonyl)phenyl
393	$SOCH_3$	2,6-diF-phenyl	1-pyrrolidinocarbonyl
394	$SOCH_3$	2,6-diF-phenyl	2-(methylsulfonyl)phenyl
395	$SOCH_3$	2,6-diF-phenyl	4-morpholino
396	$SOCH_3$	2,6-diF-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
397	$SOCH_3$	2,6-diF-phenyl	4-morpholinocarbonyl
398	$SOCH_3$	2,6-diF-phenyl	2-methyl-1-imidazolyl
399	$SOCH_3$	2,6-diF-phenyl	5-methyl-1-imidazolyl
400	$SOCH_3$	2,6-diF-phenyl	2-methylsulfonyl-1-imidazolyl
401	SO_2CH_3	phenyl	2-(aminosulfonyl)phenyl
402	SO_2CH_3	phenyl	2-(methylaminosulfonyl)phenyl
403	SO_2CH_3	phenyl	1-pyrrolidinocarbonyl
404	SO_2CH_3	phenyl	2-(methylsulfonyl)phenyl
405	SO_2CH_3	phenyl	4-morpholino
406	SO_2CH_3	phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
407	SO_2CH_3	phenyl	4-morpholinocarbonyl
408	SO_2CH_3	phenyl	2-methyl-1-imidazolyl
409	SO_2CH_3	phenyl	5-methyl-1-imidazolyl
410	SO_2CH_3	phenyl	2-methylsulfonyl-1-imidazolyl
411	SO_2CH_3	2-pyridyl	2-(aminosulfonyl)phenyl
412	SO_2CH_3	2-pyridyl	2-(methylaminosulfonyl)phenyl
413	SO_2CH_3	2-pyridyl	1-pyrrolidinocarbonyl
414	SO_2CH_3	2-pyridyl	2-(methylsulfonyl)phenyl
415	SO_2CH_3	2-pyridyl	4-morpholino
416	SO_2CH_3	2-pyridyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
417	SO_2CH_3	2-pyridyl	4-morpholinocarbonyl
418	SO_2CH_3	2-pyridyl	2-methyl-1-imidazolyl
419	SO_2CH_3	2-pyridyl	5-methyl-1-imidazolyl
420	SO_2CH_3	2-pyridyl	2-methylsulfonyl-1-imidazolyl
421	SO_2CH_3	3-pyridyl	2-(aminosulfonyl)phenyl
422	SO_2CH_3	3-pyridyl	2-(methylaminosulfonyl)phenyl
423	SO_2CH_3	3-pyridyl	1-pyrrolidinocarbonyl
424	SO_2CH_3	3-pyridyl	2-(methylsulfonyl)phenyl

425	SO_2CH_3	3-pyridyl	4-morpholino
426	SO_2CH_3	3-pyridyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
427	SO_2CH_3	3-pyridyl	4-morpholinocarbonyl
428	SO_2CH_3	3-pyridyl	2-methyl-1-imidazolyl
429	SO_2CH_3	3-pyridyl	5-methyl-1-imidazolyl
430	SO_2CH_3	3-pyridyl	2-methylsulfonyl-1-imidazolyl
431	SO_2CH_3	2-pyrimidyl	2-(aminosulfonyl)phenyl
432	SO_2CH_3	2-pyrimidyl	2-(methylaminosulfonyl)phenyl
433	SO_2CH_3	2-pyrimidyl	1-pyrrolidinocarbonyl
434	SO_2CH_3	2-pyrimidyl	2-(methylsulfonyl)phenyl
435	SO_2CH_3	2-pyrimidyl	4-morpholino
436	SO_2CH_3	2-pyrimidyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
437	SO_2CH_3	2-pyrimidyl	4-morpholinocarbonyl
438	SO_2CH_3	2-pyrimidyl	2-methyl-1-imidazolyl
439	SO_2CH_3	2-pyrimidyl	5-methyl-1-imidazolyl
440	SO_2CH_3	2-pyrimidyl	2-methylsulfonyl-1-imidazolyl
441	SO_2CH_3	5-pyrimidyl	2-(aminosulfonyl)phenyl
442	SO_2CH_3	5-pyrimidyl	2-(methylaminosulfonyl)phenyl
443	SO_2CH_3	5-pyrimidyl	1-pyrrolidinocarbonyl
444	SO_2CH_3	5-pyrimidyl	2-(methylsulfonyl)phenyl
445	SO_2CH_3	5-pyrimidyl	4-morpholino
446	SO_2CH_3	5-pyrimidyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
447	SO_2CH_3	5-pyrimidyl	4-morpholinocarbonyl
448	SO_2CH_3	5-pyrimidyl	2-methyl-1-imidazolyl
449	SO_2CH_3	5-pyrimidyl	5-methyl-1-imidazolyl
450	SO_2CH_3	5-pyrimidyl	2-methylsulfonyl-1-imidazolyl
451	SO_2CH_3	2-Cl-phenyl	2-(aminosulfonyl)phenyl
452	SO_2CH_3	2-Cl-phenyl	2-(methylaminosulfonyl)phenyl
453	SO_2CH_3	2-Cl-phenyl	1-pyrrolidinocarbonyl
454	SO_2CH_3	2-Cl-phenyl	2-(methylsulfonyl)phenyl
455	SO_2CH_3	2-Cl-phenyl	4-morpholino
456	SO_2CH_3	2-Cl-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
457	SO_2CH_3	2-Cl-phenyl	4-morpholinocarbonyl
458	SO_2CH_3	2-Cl-phenyl	2-methyl-1-imidazolyl
459	SO_2CH_3	2-Cl-phenyl	5-methyl-1-imidazolyl
460	SO_2CH_3	2-Cl-phenyl	2-methylsulfonyl-1-imidazolyl
461	SO_2CH_3	2-F-phenyl	2-(aminosulfonyl)phenyl

462	SO_2CH_3	2-F-phenyl	2-(methylaminosulfonyl)phenyl
463	SO_2CH_3	2-F-phenyl	1-pyrrolidinocarbonyl
464	SO_2CH_3	2-F-phenyl	2-(methylsulfonyl)phenyl
465	SO_2CH_3	2-F-phenyl	4-morpholino
466	SO_2CH_3	2-F-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
467	SO_2CH_3	2-F-phenyl	4-morpholinocarbonyl
468	SO_2CH_3	2-F-phenyl	2-methyl-1-imidazolyl
469	SO_2CH_3	2-F-phenyl	5-methyl-1-imidazolyl
470	SO_2CH_3	2-F-phenyl	2-methylsulfonyl-1-imidazolyl
471	SO_2CH_3	2,6-diF-phenyl	2-(aminosulfonyl)phenyl
472	SO_2CH_3	2,6-diF-phenyl	2-(methylaminosulfonyl)phenyl
473	SO_2CH_3	2,6-diF-phenyl	1-pyrrolidinocarbonyl
474	SO_2CH_3	2,6-diF-phenyl	2-(methylsulfonyl)phenyl
475	SO_2CH_3	2,6-diF-phenyl	4-morpholino
476	SO_2CH_3	2,6-diF-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
477	SO_2CH_3	2,6-diF-phenyl	4-morpholinocarbonyl
478	SO_2CH_3	2,6-diF-phenyl	2-methyl-1-imidazolyl
479	SO_2CH_3	2,6-diF-phenyl	5-methyl-1-imidazolyl
480	SO_2CH_3	2,6-diF-phenyl	2-methylsulfonyl-1-imidazolyl
481	CH_2NH-SO_2CH_3	phenyl	2-(aminosulfonyl)phenyl
482	CH_2NH-SO_2CH_3	phenyl	2-(methylaminosulfonyl)phenyl
483	CH_2NH-SO_2CH_3	phenyl	1-pyrrolidinocarbonyl
484	CH_2NH-SO_2CH_3	phenyl	2-(methylsulfonyl)phenyl
485	CH_2NH-SO_2CH_3	phenyl	4-morpholino
486	CH_2NH-SO_2CH_3	phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
487	CH_2NH-SO_2CH_3	phenyl	4-morpholinocarbonyl
488	CH_2NH-SO_2CH_3	phenyl	2-methyl-1-imidazolyl
489	CH_2NH-SO_2CH_3	phenyl	5-methyl-1-imidazolyl

490	CH_2NH-SO_2CH_3	phenyl	2-methylsulfonyl-1-imidazolyl
491	CH_2NH-SO_2CH_3	2-pyridyl	2-(aminosulfonyl)phenyl
492	CH_2NH-SO_2CH_3	2-pyridyl	2-(methylaminosulfonyl)phenyl
493	CH_2NH-SO_2CH_3	2-pyridyl	1-pyrrolidinocarbonyl
494	CH_2NH-SO_2CH_3	2-pyridyl	2-(methylsulfonyl)phenyl
495	CH_2NH-SO_2CH_3	2-pyridyl	4-morpholino
496	CH_2NH-SO_2CH_3	2-pyridyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
497	CH_2NH-SO_2CH_3	2-pyridyl	4-morpholinocarbonyl
498	CH_2NH-SO_2CH_3	2-pyridyl	2-methyl-1-imidazolyl
499	CH_2NH-SO_2CH_3	2-pyridyl	5-methyl-1-imidazolyl
500	CH_2NH-SO_2CH_3	2-pyridyl	2-methylsulfonyl-1-imidazolyl
501	CH_2NH-SO_2CH_3	3-pyridyl	2-(aminosulfonyl)phenyl
502	CH_2NH-SO_2CH_3	3-pyridyl	2-(methylaminosulfonyl)phenyl
503	CH_2NH-SO_2CH_3	3-pyridyl	1-pyrrolidinocarbonyl
504	CH_2NH-SO_2CH_3	3-pyridyl	2-(methylsulfonyl)phenyl
505	CH_2NH-SO_2CH_3	3-pyridyl	4-morpholino
506	CH_2NH-SO_2CH_3	3-pyridyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
507	CH_2NH-SO_2CH_3	3-pyridyl	4-morpholinocarbonyl

508	CH_2NH-SO_2CH_3	3-pyridyl	2-methyl-1-imidazolyl
509	CH_2NH-SO_2CH_3	3-pyridyl	5-methyl-1-imidazolyl
510	CH_2NH-SO_2CH_3	3-pyridyl	2-methylsulfonyl-1-imidazolyl
511	CH_2NH-SO_2CH_3	2-pyrimidyl	2-(aminosulfonyl)phenyl
512	CH_2NH-SO_2CH_3	2-pyrimidyl	2-(methylaminosulfonyl)phenyl
513	CH_2NH-SO_2CH_3	2-pyrimidyl	1-pyrrolidinocarbonyl
514	CH_2NH-SO_2CH_3	2-pyrimidyl	2-(methylsulfonyl)phenyl
515	CH_2NH-SO_2CH_3	2-pyrimidyl	4-morpholino
516	CH_2NH-SO_2CH_3	2-pyrimidyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
517	CH_2NH-SO_2CH_3	2-pyrimidyl	4-morpholinocarbonyl
518	CH_2NH-SO_2CH_3	2-pyrimidyl	2-methyl-1-imidazolyl
519	CH_2NH-SO_2CH_3	2-pyrimidyl	5-methyl-1-imidazolyl
520	CH_2NH-SO_2CH_3	2-pyrimidyl	2-methylsulfonyl-1-imidazolyl
521	CH_2NH-SO_2CH_3	5-pyrimidyl	2-(aminosulfonyl)phenyl
522	CH_2NH-SO_2CH_3	5-pyrimidyl	2-(methylaminosulfonyl)phenyl
523	CH_2NH-SO_2CH_3	5-pyrimidyl	1-pyrrolidinocarbonyl
524	CH_2NH-SO_2CH_3	5-pyrimidyl	2-(methylsulfonyl)phenyl
525	CH_2NH-SO_2CH_3	5-pyrimidyl	4-morpholino

526	CH_2NH-SO_2CH_3	5-pyrimidyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
527	CH_2NH-SO_2CH_3	5-pyrimidyl	4-morpholinocarbonyl
528	CH_2NH-SO_2CH_3	5-pyrimidyl	2-methyl-1-imidazolyl
529	CH_2NH-SO_2CH_3	5-pyrimidyl	5-methyl-1-imidazolyl
530	CH_2NH-SO_2CH_3	5-pyrimidyl	2-methylsulfonyl-1-imidazolyl
531	CH_2NH-SO_2CH_3	2-Cl-phenyl	2-(aminosulfonyl)phenyl
532	CH_2NH-SO_2CH_3	2-Cl-phenyl	2-(methylaminosulfonyl)phenyl
533	CH_2NH-SO_2CH_3	2-Cl-phenyl	1-pyrrolidinocarbonyl
534	CH_2NH-SO_2CH_3	2-Cl-phenyl	2-(methylsulfonyl)phenyl
535	CH_2NH-SO_2CH_3	2-Cl-phenyl	4-morpholino
536	CH_2NH-SO_2CH_3	2-Cl-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
537	CH_2NH-SO_2CH_3	2-Cl-phenyl	4-morpholinocarbonyl
538	CH_2NH-SO_2CH_3	2-Cl-phenyl	2-methyl-1-imidazolyl
539	CH_2NH-SO_2CH_3	2-Cl-phenyl	5-methyl-1-imidazolyl
540	CH_2NH-SO_2CH_3	2-Cl-phenyl	2-methylsulfonyl-1-imidazolyl
541	CH_2NH-SO_2CH_3	2-F-phenyl	2-(aminosulfonyl)phenyl
542	CH_2NH-SO_2CH_3	2-F-phenyl	2-(methylaminosulfonyl)phenyl
543	CH_2NH-SO_2CH_3	2-F-phenyl	1-pyrrolidinocarbonyl

544	CH_2NH-SO_2CH_3	2-F-phenyl	2-(methylsulfonyl)phenyl
545	CH_2NH-SO_2CH_3	2-F-phenyl	4-morpholino
546	CH_2NH-SO_2CH_3	2-F-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
547	CH_2NH-SO_2CH_3	2-F-phenyl	4-morpholinocarbonyl
548	CH_2NH-SO_2CH_3	2-F-phenyl	2-methyl-1-imidazolyl
549	CH_2NH-SO_2CH_3	2-F-phenyl	5-methyl-1-imidazolyl
550	CH_2NH-SO_2CH_3	2-F-phenyl	2-methylsulfonyl-1-imidazolyl
551	CH_2NH-SO_2CH_3	2,6-diF-phenyl	2-(aminosulfonyl)phenyl
552	CH_2NH-SO_2CH_3	2,6-diF-phenyl	2-(methylaminosulfonyl)phenyl
553	CH_2NH-SO_2CH_3	2,6-diF-phenyl	1-pyrrolidinocarbonyl
554	CH_2NH-SO_2CH_3	2,6-diF-phenyl	2-(methylsulfonyl)phenyl
555	CH_2NH-SO_2CH_3	2,6-diF-phenyl	4-morpholino
556	CH_2NH-SO_2CH_3	2,6-diF-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
557	CH_2NH-SO_2CH_3	2,6-diF-phenyl	4-morpholinocarbonyl
558	CH_2NH-SO_2CH_3	2,6-diF-phenyl	2-methyl-1-imidazolyl
559	CH_2NH-SO_2CH_3	2,6-diF-phenyl	5-methyl-1-imidazolyl
560	CH_2NH-SO_2CH_3	2,6-diF-phenyl	2-methylsulfonyl-1-imidazolyl
561	Cl	phenyl	2-(aminosulfonyl)phenyl
562	Cl	phenyl	2-(methylaminosulfonyl)phenyl
563	Cl	phenyl	1-pyrrolidinocarbonyl

564	Cl	phenyl	2-(methylsulfonyl)phenyl
565	Cl	phenyl	4-morpholino
566	Cl	phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
567	Cl	phenyl	4-morpholinocarbonyl
568	Cl	phenyl	2-methyl-1-imidazolyl
569	Cl	phenyl	5-methyl-1-imidazolyl
570	Cl	phenyl	2-methylsulfonyl-1-imidazolyl
571	Cl	2-pyridyl	2-(aminosulfonyl)phenyl
572	Cl	2-pyridyl	2-(methylaminosulfonyl)phenyl
573	Cl	2-pyridyl	1-pyrrolidinocarbonyl
574	Cl	2-pyridyl	2-(methylsulfonyl)phenyl
575	Cl	2-pyridyl	4-morpholino
576	Cl	2-pyridyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
577	Cl	2-pyridyl	4-morpholinocarbonyl
578	Cl	2-pyridyl	2-methyl-1-imidazolyl
579	Cl	2-pyridyl	5-methyl-1-imidazolyl
580	Cl	2-pyridyl	2-methylsulfonyl-1-imidazolyl
581	Cl	3-pyridyl	2-(aminosulfonyl)phenyl
582	Cl	3-pyridyl	2-(methylaminosulfonyl)phenyl
583	Cl	3-pyridyl	1-pyrrolidinocarbonyl
584	Cl	3-pyridyl	2-(methylsulfonyl)phenyl
585	Cl	3-pyridyl	4-morpholino
586	Cl	3-pyridyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
587	Cl	3-pyridyl	4-morpholinocarbonyl
588	Cl	3-pyridyl	2-methyl-1-imidazolyl
589	Cl	3-pyridyl	5-methyl-1-imidazolyl
590	Cl	3-pyridyl	2-methylsulfonyl-1-imidazolyl
591	Cl	2-pyrimidyl	2-(aminosulfonyl)phenyl
592	Cl	2-pyrimidyl	2-(methylaminosulfonyl)phenyl
593	Cl	2-pyrimidyl	1-pyrrolidinocarbonyl
594	Cl	2-pyrimidyl	2-(methylsulfonyl)phenyl
595	Cl	2-pyrimidyl	4-morpholino
596	Cl	2-pyrimidyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
597	Cl	2-pyrimidyl	4-morpholinocarbonyl
598	Cl	2-pyrimidyl	2-methyl-1-imidazolyl
599	Cl	2-pyrimidyl	5-methyl-1-imidazolyl
600	Cl	2-pyrimidyl	2-methylsulfonyl-1-imidazolyl

601	Cl	5-pyrimidyl	2-(aminosulfonyl)phenyl
602	Cl	5-pyrimidyl	2-(methylaminosulfonyl)phenyl
603	Cl	5-pyrimidyl	1-pyrrolidinocarbonyl
604	Cl	5-pyrimidyl	2-(methylsulfonyl)phenyl
605	Cl	5-pyrimidyl	4-morpholino
606	Cl	5-pyrimidyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
607	Cl	5-pyrimidyl	4-morpholinocarbonyl
608	Cl	5-pyrimidyl	2-methyl-1-imidazolyl
609	Cl	5-pyrimidyl	5-methyl-1-imidazolyl
610	Cl	5-pyrimidyl	2-methylsulfonyl-1-imidazolyl
611	Cl	2-Cl-phenyl	2-(aminosulfonyl)phenyl
612	Cl	2-Cl-phenyl	2-(methylaminosulfonyl)phenyl
613	Cl	2-Cl-phenyl	1-pyrrolidinocarbonyl
614	Cl	2-Cl-phenyl	2-(methylsulfonyl)phenyl
615	Cl	2-Cl-phenyl	4-morpholino
616	Cl	2-Cl-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
617	Cl	2-Cl-phenyl	4-morpholinocarbonyl
618	Cl	2-Cl-phenyl	2-methyl-1-imidazolyl
619	Cl	2-Cl-phenyl	5-methyl-1-imidazolyl
620	Cl	2-Cl-phenyl	2-methylsulfonyl-1-imidazolyl
621	Cl	2-F-phenyl	2-(aminosulfonyl)phenyl
622	Cl	2-F-phenyl	2-(methylaminosulfonyl)phenyl
623	Cl	2-F-phenyl	1-pyrrolidinocarbonyl
624	Cl	2-F-phenyl	2-(methylsulfonyl)phenyl
625	Cl	2-F-phenyl	4-morpholino
626	Cl	2-F-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
627	Cl	2-F-phenyl	4-morpholinocarbonyl
628	Cl	2-F-phenyl	2-methyl-1-imidazolyl
629	Cl	2-F-phenyl	5-methyl-1-imidazolyl
630	Cl	2-F-phenyl	2-methylsulfonyl-1-imidazolyl
631	Cl	2,6-diF-phenyl	2-(aminosulfonyl)phenyl
632	Cl	2,6-diF-phenyl	2-(methylaminosulfonyl)phenyl
633	Cl	2,6-diF-phenyl	1-pyrrolidinocarbonyl
634	Cl	2,6-diF-phenyl	2-(methylsulfonyl)phenyl
635	Cl	2,6-diF-phenyl	4-morpholino
636	Cl	2,6-diF-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
637	Cl	2,6-diF-phenyl	4-morpholinocarbonyl

638	Cl	2,6-diF-phenyl	2-methyl-1-imidazolyl
639	Cl	2,6-diF-phenyl	5-methyl-1-imidazolyl
640	Cl	2,6-diF-phenyl	2-methylsulfonyl-1-imidazolyl
641	F	phenyl	2-(aminosulfonyl)phenyl
642	F	phenyl	2-(methylaminosulfonyl)phenyl
643	F	phenyl	1-pyrrolidinocarbonyl
644	F	phenyl	2-(methylsulfonyl)phenyl
645	F	phenyl	4-morpholino
646	F	phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
647	F	phenyl	4-morpholinocarbonyl
648	F	phenyl	2-methyl-1-imidazolyl
649	F	phenyl	5-methyl-1-imidazolyl
650	F	phenyl	2-methylsulfonyl-1-imidazolyl
651	F	2-pyridyl	2-(aminosulfonyl)phenyl
652	F	2-pyridyl	2-(methylaminosulfonyl)phenyl
653	F	2-pyridyl	1-pyrrolidinocarbonyl
654	F	2-pyridyl	2-(methylsulfonyl)phenyl
655	F	2-pyridyl	4-morpholino
656	F	2-pyridyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
657	F	2-pyridyl	4-morpholinocarbonyl
658	F	2-pyridyl	2-methyl-1-imidazolyl
659	F	2-pyridyl	5-methyl-1-imidazolyl
660	F	2-pyridyl	2-methylsulfonyl-1-imidazolyl
661	F	3-pyridyl	2-(aminosulfonyl)phenyl
662	F	3-pyridyl	2-(methylaminosulfonyl)phenyl
663	F	3-pyridyl	1-pyrrolidinocarbonyl
664	F	3-pyridyl	2-(methylsulfonyl)phenyl
665	F	3-pyridyl	4-morpholino
666	F	3-pyridyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
667	F	3-pyridyl	4-morpholinocarbonyl
668	F	3-pyridyl	2-methyl-1-imidazolyl
669	F	3-pyridyl	5-methyl-1-imidazolyl
670	F	3-pyridyl	2-methylsulfonyl-1-imidazolyl
671	F	2-pyrimidyl	2-(aminosulfonyl)phenyl
672	F	2-pyrimidyl	2-(methylaminosulfonyl)phenyl
673	F	2-pyrimidyl	1-pyrrolidinocarbonyl
674	F	2-pyrimidyl	2-(methylsulfonyl)phenyl

675	F	2-pyrimidyl	4-morpholino
676	F	2-pyrimidyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
677	F	2-pyrimidyl	4-morpholinocarbonyl
678	F	2-pyrimidyl	2-methyl-1-imidazolyl
679	F	2-pyrimidyl	5-methyl-1-imidazolyl
680	F	2-pyrimidyl	2-methylsulfonyl-1-imidazolyl
681	F	5-pyrimidyl	2-(aminosulfonyl)phenyl
682	F	5-pyrimidyl	2-(methylaminosulfonyl)phenyl
683	F	5-pyrimidyl	1-pyrrolidinocarbonyl
684	F	5-pyrimidyl	2-(methylsulfonyl)phenyl
685	F	5-pyrimidyl	4-morpholino
686	F	5-pyrimidyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
687	F	5-pyrimidyl	4-morpholinocarbonyl
688	F	5-pyrimidyl	2-methyl-1-imidazolyl
689	F	5-pyrimidyl	5-methyl-1-imidazolyl
690	F	5-pyrimidyl	2-methylsulfonyl-1-imidazolyl
691	F	2-Cl-phenyl	2-(aminosulfonyl)phenyl
692	F	2-Cl-phenyl	2-(methylaminosulfonyl)phenyl
693	F	2-Cl-phenyl	1-pyrrolidinocarbonyl
694	F	2-Cl-phenyl	2-(methylsulfonyl)phenyl
695	F	2-Cl-phenyl	4-morpholino
696	F	2-Cl-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
697	F	2-Cl-phenyl	4-morpholinocarbonyl
698	F	2-Cl-phenyl	2-methyl-1-imidazolyl
699	F	2-Cl-phenyl	5-methyl-1-imidazolyl
700	F	2-Cl-phenyl	2-methylsulfonyl-1-imidazolyl
701	F	2-F-phenyl	2-(aminosulfonyl)phenyl
702	F	2-F-phenyl	2-(methylaminosulfonyl)phenyl
703	F	2-F-phenyl	1-pyrrolidinocarbonyl
704	F	2-F-phenyl	2-(methylsulfonyl)phenyl
705	F	2-F-phenyl	4-morpholino
706	F	2-F-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
707	F	2-F-phenyl	4-morpholinocarbonyl
708	F	2-F-phenyl	2-methyl-1-imidazolyl
709	F	2-F-phenyl	5-methyl-1-imidazolyl
710	F	2-F-phenyl	2-methylsulfonyl-1-imidazolyl
711	F	2,6-diF-phenyl	2-(aminosulfonyl)phenyl

712	F	2,6-diF-phenyl	2-(methylaminosulfonyl)phenyl
713	F	2,6-diF-phenyl	1-pyrrolidinocarbonyl
714	F	2,6-diF-phenyl	2-(methylsulfonyl)phenyl
715	F	2,6-diF-phenyl	4-morpholino
716	F	2,6-diF-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
717	F	2,6-diF-phenyl	4-morpholinocarbonyl
718	F	2,6-diF-phenyl	2-methyl-1-imidazolyl
719	F	2,6-diF-phenyl	5-methyl-1-imidazolyl
720	F	2,6-diF-phenyl	2-methylsulfonyl-1-imidazolyl
721	CO_2CH_3	phenyl	2-(aminosulfonyl)phenyl
722	CO_2CH_3	phenyl	2-(methylaminosulfonyl)phenyl
723	CO_2CH_3	phenyl	1-pyrrolidinocarbonyl
724	CO_2CH_3	phenyl	2-(methylsulfonyl)phenyl
725	CO_2CH_3	phenyl	4-morpholino
726	CO_2CH_3	phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
727	CO_2CH_3	phenyl	4-morpholinocarbonyl
728	CO_2CH_3	phenyl	2-methyl-1-imidazolyl
729	CO_2CH_3	phenyl	5-methyl-1-imidazolyl
730	CO_2CH_3	phenyl	2-methylsulfonyl-1-imidazolyl
731	CO_2CH_3	2-pyridyl	2-(aminosulfonyl)phenyl
732	CO_2CH_3	2-pyridyl	2-(methylaminosulfonyl)phenyl
733	CO_2CH_3	2-pyridyl	1-pyrrolidinocarbonyl
734	CO_2CH_3	2-pyridyl	2-(methylsulfonyl)phenyl
735	CO_2CH_3	2-pyridyl	4-morpholino
736	CO_2CH_3	2-pyridyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
737	CO_2CH_3	2-pyridyl	4-morpholinocarbonyl
738	CO_2CH_3	2-pyridyl	2-methyl-1-imidazolyl
739	CO_2CH_3	2-pyridyl	5-methyl-1-imidazolyl
740	CO_2CH_3	2-pyridyl	2-methylsulfonyl-1-imidazolyl
741	CO_2CH_3	3-pyridyl	2-(aminosulfonyl)phenyl
742	CO_2CH_3	3-pyridyl	2-(methylaminosulfonyl)phenyl
743	CO_2CH_3	3-pyridyl	1-pyrrolidinocarbonyl
744	CO_2CH_3	3-pyridyl	2-(methylsulfonyl)phenyl
745	CO_2CH_3	3-pyridyl	4-morpholino
746	CO_2CH_3	3-pyridyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
747	CO_2CH_3	3-pyridyl	4-morpholinocarbonyl
748	CO_2CH_3	3-pyridyl	2-methyl-1-imidazolyl

749	CO_2CH_3	3-pyridyl	5-methyl-1-imidazolyl
750	CO_2CH_3	3-pyridyl	2-methylsulfonyl-1-imidazolyl
751	CO_2CH_3	2-pyrimidyl	2-(aminosulfonyl)phenyl
752	CO_2CH_3	2-pyrimidyl	2-(methylaminosulfonyl)phenyl
753	CO_2CH_3	2-pyrimidyl	1-pyrrolidinocarbonyl
754	CO_2CH_3	2-pyrimidyl	2-(methylsulfonyl)phenyl
755	CO_2CH_3	2-pyrimidyl	4-morpholino
756	CO_2CH_3	2-pyrimidyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
757	CO_2CH_3	2-pyrimidyl	4-morpholinocarbonyl
758	CO_2CH_3	2-pyrimidyl	2-methyl-1-imidazolyl
759	CO_2CH_3	2-pyrimidyl	5-methyl-1-imidazolyl
760	CO_2CH_3	2-pyrimidyl	2-methylsulfonyl-1-imidazolyl
761	CO_2CH_3	5-pyrimidyl	2-(aminosulfonyl)phenyl
762	CO_2CH_3	5-pyrimidyl	2-(methylaminosulfonyl)phenyl
763	CO_2CH_3	5-pyrimidyl	1-pyrrolidinocarbonyl
764	CO_2CH_3	5-pyrimidyl	2-(methylsulfonyl)phenyl
765	CO_2CH_3	5-pyrimidyl	4-morpholino
766	CO_2CH_3	5-pyrimidyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
767	CO_2CH_3	5-pyrimidyl	4-morpholinocarbonyl
768	CO_2CH_3	5-pyrimidyl	2-methyl-1-imidazolyl
769	CO_2CH_3	5-pyrimidyl	5-methyl-1-imidazolyl
770	CO_2CH_3	5-pyrimidyl	2-methylsulfonyl-1-imidazolyl
771	CO_2CH_3	2-Cl-phenyl	2-(aminosulfonyl)phenyl
772	CO_2CH_3	2-Cl-phenyl	2-(methylaminosulfonyl)phenyl
773	CO_2CH_3	2-Cl-phenyl	1-pyrrolidinocarbonyl
774	CO_2CH_3	2-Cl-phenyl	2-(methylsulfonyl)phenyl
775	CO_2CH_3	2-Cl-phenyl	4-morpholino
776	CO_2CH_3	2-Cl-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
777	CO_2CH_3	2-Cl-phenyl	4-morpholinocarbonyl
778	CO_2CH_3	2-Cl-phenyl	2-methyl-1-imidazolyl
779	CO_2CH_3	2-Cl-phenyl	5-methyl-1-imidazolyl
780	CO_2CH_3	2-Cl-phenyl	2-methylsulfonyl-1-imidazolyl
781	CO_2CH_3	2-F-phenyl	2-(aminosulfonyl)phenyl
782	CO_2CH_3	2-F-phenyl	2-(methylaminosulfonyl)phenyl
783	CO_2CH_3	2-F-phenyl	1-pyrrolidinocarbonyl
784	CO_2CH_3	2-F-phenyl	2-(methylsulfonyl)phenyl
785	CO_2CH_3	2-F-phenyl	4-morpholino

786	CO_2CH_3	2-F-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
787	CO_2CH_3	2-F-phenyl	4-morpholinocarbonyl
788	CO_2CH_3	2-F-phenyl	2-methyl-1-imidazolyl
789	CO_2CH_3	2-F-phenyl	5-methyl-1-imidazolyl
790	CO_2CH_3	2-F-phenyl	2-methylsulfonyl-1-imidazolyl
791	CO_2CH_3	2,6-diF-phenyl	2-(aminosulfonyl)phenyl
792	CO_2CH_3	2,6-diF-phenyl	2-(methylaminosulfonyl)phenyl
793	CO_2CH_3	2,6-diF-phenyl	1-pyrrolidinocarbonyl
794	CO_2CH_3	2,6-diF-phenyl	2-(methylsulfonyl)phenyl
795	CO_2CH_3	2,6-diF-phenyl	4-morpholino
796	CO_2CH_3	2,6-diF-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
797	CO_2CH_3	2,6-diF-phenyl	4-morpholinocarbonyl
798	CO_2CH_3	2,6-diF-phenyl	2-methyl-1-imidazolyl
799	CO_2CH_3	2,6-diF-phenyl	5-methyl-1-imidazolyl
800	CO_2CH_3	2,6-diF-phenyl	2-methylsulfonyl-1-imidazolyl
801	CH_2OCH_3	phenyl	2-(aminosulfonyl)phenyl
802	CH_2OCH_3	phenyl	2-(methylaminosulfonyl)phenyl
803	CH_2OCH_3	phenyl	1-pyrrolidinocarbonyl
804	CH_2OCH_3	phenyl	2-(methylsulfonyl)phenyl
805	CH_2OCH_3	phenyl	4-morpholino
806	CH_2OCH_3	phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
807	CH_2OCH_3	phenyl	4-morpholinocarbonyl
808	CH_2OCH_3	phenyl	2-methyl-1-imidazolyl
809	CH_2OCH_3	phenyl	5-methyl-1-imidazolyl
810	CH_2OCH_3	phenyl	2-methylsulfonyl-1-imidazolyl
811	CH_2OCH_3	2-pyridyl	2-(aminosulfonyl)phenyl
812	CH_2OCH_3	2-pyridyl	2-(methylaminosulfonyl)phenyl
813	CH_2OCH_3	2-pyridyl	1-pyrrolidinocarbonyl
814	CH_2OCH_3	2-pyridyl	2-(methylsulfonyl)phenyl
815	CH_2OCH_3	2-pyridyl	4-morpholino
816	CH_2OCH_3	2-pyridyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
817	CH_2OCH_3	2-pyridyl	4-morpholinocarbonyl
818	CH_2OCH_3	2-pyridyl	2-methyl-1-imidazolyl
819	CH_2OCH_3	2-pyridyl	5-methyl-1-imidazolyl
820	CH_2OCH_3	2-pyridyl	2-methylsulfonyl-1-imidazolyl
821	CH_2OCH_3	3-pyridyl	2-(aminosulfonyl)phenyl
822	CH_2OCH_3	3-pyridyl	2-(methylaminosulfonyl)phenyl

823	CH_2OCH_3	3-pyridyl	1-pyrrolidinocarbonyl
824	CH_2OCH_3	3-pyridyl	2-(methylsulfonyl)phenyl
825	CH_2OCH_3	3-pyridyl	4-morpholino
826	CH_2OCH_3	3-pyridyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
827	CH_2OCH_3	3-pyridyl	4-morpholinocarbonyl
828	CH_2OCH_3	3-pyridyl	2-methyl-1-imidazolyl
829	CH_2OCH_3	3-pyridyl	5-methyl-1-imidazolyl
830	CH_2OCH_3	3-pyridyl	2-methylsulfonyl-1-imidazolyl
831	CH_2OCH_3	2-pyrimidyl	2-(aminosulfonyl)phenyl
832	CH_2OCH_3	2-pyrimidyl	2-(methylaminosulfonyl)phenyl
833	CH_2OCH_3	2-pyrimidyl	1-pyrrolidinocarbonyl
834	CH_2OCH_3	2-pyrimidyl	2-(methylsulfonyl)phenyl
835	CH_2OCH_3	2-pyrimidyl	4-morpholino
836	CH_2OCH_3	2-pyrimidyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
837	CH_2OCH_3	2-pyrimidyl	4-morpholinocarbonyl
838	CH_2OCH_3	2-pyrimidyl	2-methyl-1-imidazolyl
839	CH_2OCH_3	2-pyrimidyl	5-methyl-1-imidazolyl
840	CH_2OCH_3	2-pyrimidyl	2-methylsulfonyl-1-imidazolyl
841	CH_2OCH_3	5-pyrimidyl	2-(aminosulfonyl)phenyl
842	CH_2OCH_3	5-pyrimidyl	2-(methylaminosulfonyl)phenyl
843	CH_2OCH_3	5-pyrimidyl	1-pyrrolidinocarbonyl
844	CH_2OCH_3	5-pyrimidyl	2-(methylsulfonyl)phenyl
845	CH_2OCH_3	5-pyrimidyl	4-morpholino
846	CH_2OCH_3	5-pyrimidyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
847	CH_2OCH_3	5-pyrimidyl	4-morpholinocarbonyl
848	CH_2OCH_3	5-pyrimidyl	2-methyl-1-imidazolyl
849	CH_2OCH_3	5-pyrimidyl	5-methyl-1-imidazolyl
850	CH_2OCH_3	5-pyrimidyl	2-methylsulfonyl-1-imidazolyl
851	CH_2OCH_3	2-Cl-phenyl	2-(aminosulfonyl)phenyl
852	CH_2OCH_3	2-Cl-phenyl	2-(methylaminosulfonyl)phenyl
853	CH_2OCH_3	2-Cl-phenyl	1-pyrrolidinocarbonyl
854	CH_2OCH_3	2-Cl-phenyl	2-(methylsulfonyl)phenyl
855	CH_2OCH_3	2-Cl-phenyl	4-morpholino
856	CH_2OCH_3	2-Cl-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
857	CH_2OCH_3	2-Cl-phenyl	4-morpholinocarbonyl
858	CH_2OCH_3	2-Cl-phenyl	2-methyl-1-imidazolyl
859	CH_2OCH_3	2-Cl-phenyl	5-methyl-1-imidazolyl

860	CH_2OCH_3	2-Cl-phenyl	2-methylsulfonyl-1-imidazolyl
861	CH_2OCH_3	2-F-phenyl	2-(aminosulfonyl)phenyl
862	CH_2OCH_3	2-F-phenyl	2-(methylaminosulfonyl)phenyl
863	CH_2OCH_3	2-F-phenyl	1-pyrrolidinocarbonyl
864	CH_2OCH_3	2-F-phenyl	2-(methylsulfonyl)phenyl
865	CH_2OCH_3	2-F-phenyl	4-morpholino
866	CH_2OCH_3	2-F-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
867	CH_2OCH_3	2-F-phenyl	4-morpholinocarbonyl
868	CH_2OCH_3	2-F-phenyl	2-methyl-1-imidazolyl
869	CH_2OCH_3	2-F-phenyl	5-methyl-1-imidazolyl
870	CH_2OCH_3	2-F-phenyl	2-methylsulfonyl-1-imidazolyl
871	CH_2OCH_3	2,6-diF-phenyl	2-(aminosulfonyl)phenyl
872	CH_2OCH_3	2,6-diF-phenyl	2-(methylaminosulfonyl)phenyl
873	CH_2OCH_3	2,6-diF-phenyl	1-pyrrolidinocarbonyl
874	CH_2OCH_3	2,6-diF-phenyl	2-(methylsulfonyl)phenyl
875	CH_2OCH_3	2,6-diF-phenyl	4-morpholino
876	CH_2OCH_3	2,6-diF-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
877	CH_2OCH_3	2,6-diF-phenyl	4-morpholinocarbonyl
878	CH_2OCH_3	2,6-diF-phenyl	2-methyl-1-imidazolyl
879	CH_2OCH_3	2,6-diF-phenyl	5-methyl-1-imidazolyl
880	CH_2OCH_3	2,6-diF-phenyl	2-methylsulfonyl-1-imidazolyl
881	$CONH_2$	phenyl	2-(aminosulfonyl)phenyl
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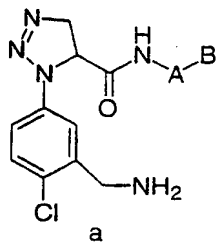
883	$CONH_2$	phenyl	1-pyrrolidinocarbonyl
884	$CONH_2$	phenyl	2-(methylsulfonyl)phenyl
885	$CONH_2$	phenyl	4-morpholino
886	$CONH_2$	phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
887	$CONH_2$	phenyl	4-morpholinocarbonyl
888	$CONH_2$	phenyl	2-methyl-1-imidazolyl
889	$CONH_2$	phenyl	5-methyl-1-imidazolyl
890	$CONH_2$	phenyl	2-methylsulfonyl-1-imidazolyl
891	$CONH_2$	2-pyridyl	2-(aminosulfonyl)phenyl
892	$CONH_2$	2-pyridyl	2-(methylaminosulfonyl)phenyl
893	$CONH_2$	2-pyridyl	1-pyrrolidinocarbonyl
894	$CONH_2$	2-pyridyl	2-(methylsulfonyl)phenyl
895	$CONH_2$	2-pyridyl	4-morpholino
896	$CONH_2$	2-pyridyl	2-(1'-CF_3-tetrazol-2-yl)phenyl

897	$CONH_2$	2-pyridyl	4-morpholinocarbonyl
898	$CONH_2$	2-pyridyl	2-methyl-1-imidazolyl
899	$CONH_2$	2-pyridyl	5-methyl-1-imidazolyl
900	$CONH_2$	2-pyridyl	2-methylsulfonyl-1-imidazolyl
901	$CONH_2$	3-pyridyl	2-(aminosulfonyl)phenyl
902	$CONH_2$	3-pyridyl	2-(methylaminosulfonyl)phenyl
903	$CONH_2$	3-pyridyl	1-pyrrolidinocarbonyl
904	$CONH_2$	3-pyridyl	2-(methylsulfonyl)phenyl
905	$CONH_2$	3-pyridyl	4-morpholino
906	$CONH_2$	3-pyridyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
907	$CONH_2$	3-pyridyl	4-morpholinocarbonyl
908	$CONH_2$	3-pyridyl	2-methyl-1-imidazolyl
909	$CONH_2$	3-pyridyl	5-methyl-1-imidazolyl
910	$CONH_2$	3-pyridyl	2-methylsulfonyl-1-imidazolyl
911	$CONH_2$	2-pyrimidyl	2-(aminosulfonyl)phenyl
912	$CONH_2$	2-pyrimidyl	2-(methylaminosulfonyl)phenyl
913	$CONH_2$	2-pyrimidyl	1-pyrrolidinocarbonyl
914	$CONH_2$	2-pyrimidyl	2-(methylsulfonyl)phenyl
915	$CONH_2$	2-pyrimidyl	4-morpholino
916	$CONH_2$	2-pyrimidyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
917	$CONH_2$	2-pyrimidyl	4-morpholinocarbonyl
918	$CONH_2$	2-pyrimidyl	2-methyl-1-imidazolyl
919	$CONH_2$	2-pyrimidyl	5-methyl-1-imidazolyl
920	$CONH_2$	2-pyrimidyl	2-methylsulfonyl-1-imidazolyl
921	$CONH_2$	5-pyrimidyl	2-(aminosulfonyl)phenyl
922	$CONH_2$	5-pyrimidyl	2-(methylaminosulfonyl)phenyl
923	$CONH_2$	5-pyrimidyl	1-pyrrolidinocarbonyl
924	$CONH_2$	5-pyrimidyl	2-(methylsulfonyl)phenyl
925	$CONH_2$	5-pyrimidyl	4-morpholino
926	$CONH_2$	5-pyrimidyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
927	$CONH_2$	5-pyrimidyl	4-morpholinocarbonyl
928	$CONH_2$	5-pyrimidyl	2-methyl-1-imidazolyl
929	$CONH_2$	5-pyrimidyl	5-methyl-1-imidazolyl
930	$CONH_2$	5-pyrimidyl	2-methylsulfonyl-1-imidazolyl
931	$CONH_2$	2-Cl-phenyl	2-(aminosulfonyl)phenyl
932	$CONH_2$	2-Cl-phenyl	2-(methylaminosulfonyl)phenyl
933	$CONH_2$	2-Cl-phenyl	1-pyrrolidinocarbonyl

934	$CONH_2$	2-Cl-phenyl	2-(methylsulfonyl)phenyl
935	$CONH_2$	2-Cl-phenyl	4-morpholino
936	$CONH_2$	2-Cl-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
937	$CONH_2$	2-Cl-phenyl	4-morpholinocarbonyl
938	$CONH_2$	2-Cl-phenyl	2-methyl-1-imidazolyl
939	$CONH_2$	2-Cl-phenyl	5-methyl-1-imidazolyl
940	$CONH_2$	2-Cl-phenyl	2-methylsulfonyl-1-imidazolyl
941	$CONH_2$	2-F-phenyl	2-(aminosulfonyl)phenyl
942	$CONH_2$	2-F-phenyl	2-(methylaminosulfonyl)phenyl
943	$CONH_2$	2-F-phenyl	1-pyrrolidinocarbonyl
944	$CONH_2$	2-F-phenyl	2-(methylsulfonyl)phenyl
945	$CONH_2$	2-F-phenyl	4-morpholino
946	$CONH_2$	2-F-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
947	$CONH_2$	2-F-phenyl	4-morpholinocarbonyl
948	$CONH_2$	2-F-phenyl	2-methyl-1-imidazolyl
949	$CONH_2$	2-F-phenyl	5-methyl-1-imidazolyl
950	$CONH_2$	2-F-phenyl	2-methylsulfonyl-1-imidazolyl
951	$CONH_2$	2,6-diF-phenyl	2-(aminosulfonyl)phenyl
952	$CONH_2$	2,6-diF-phenyl	2-(methylaminosulfonyl)phenyl
953	$CONH_2$	2,6-diF-phenyl	1-pyrrolidinocarbonyl
954	$CONH_2$	2,6-diF-phenyl	2-(methylsulfonyl)phenyl
955	$CONH_2$	2,6-diF-phenyl	4-morpholino
956	$CONH_2$	2,6-diF-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
957	$CONH_2$	2,6-diF-phenyl	4-morpholinocarbonyl
958	$CONH_2$	2,6-diF-phenyl	2-methyl-1-imidazolyl
959	$CONH_2$	2,6-diF-phenyl	5-methyl-1-imidazolyl
960	$CONH_2$	2,6-diF-phenyl	2-methylsulfonyl-1-imidazolyl

Table 2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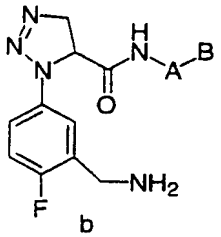
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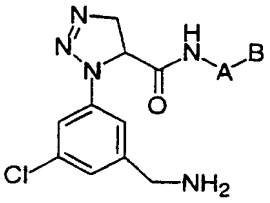
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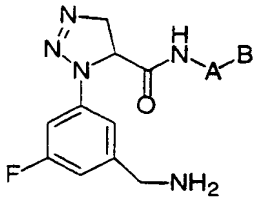
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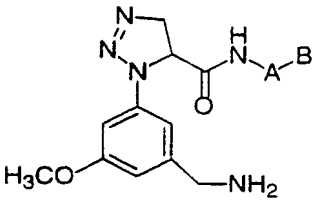
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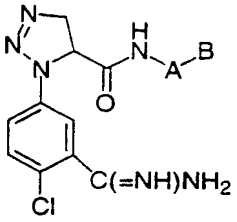
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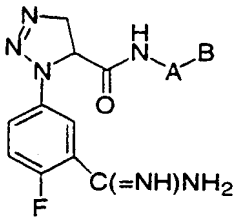
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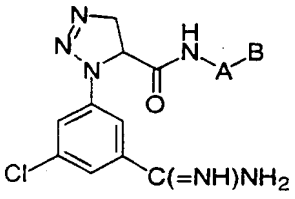
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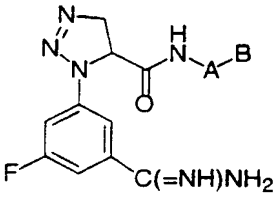
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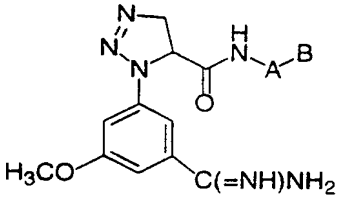
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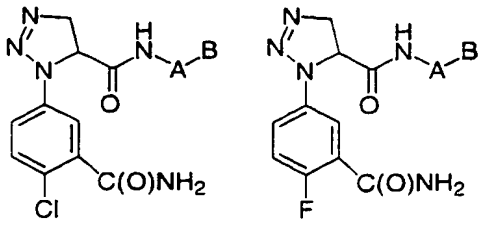

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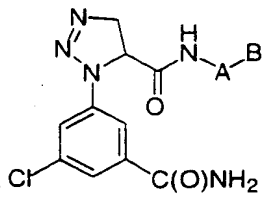

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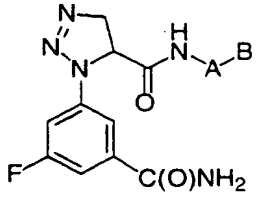

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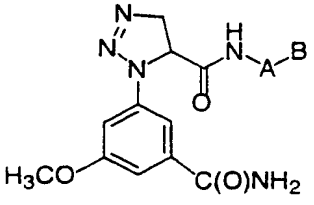

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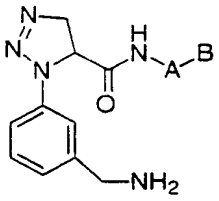

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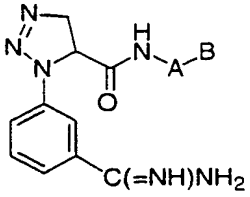

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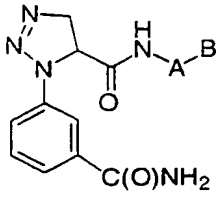

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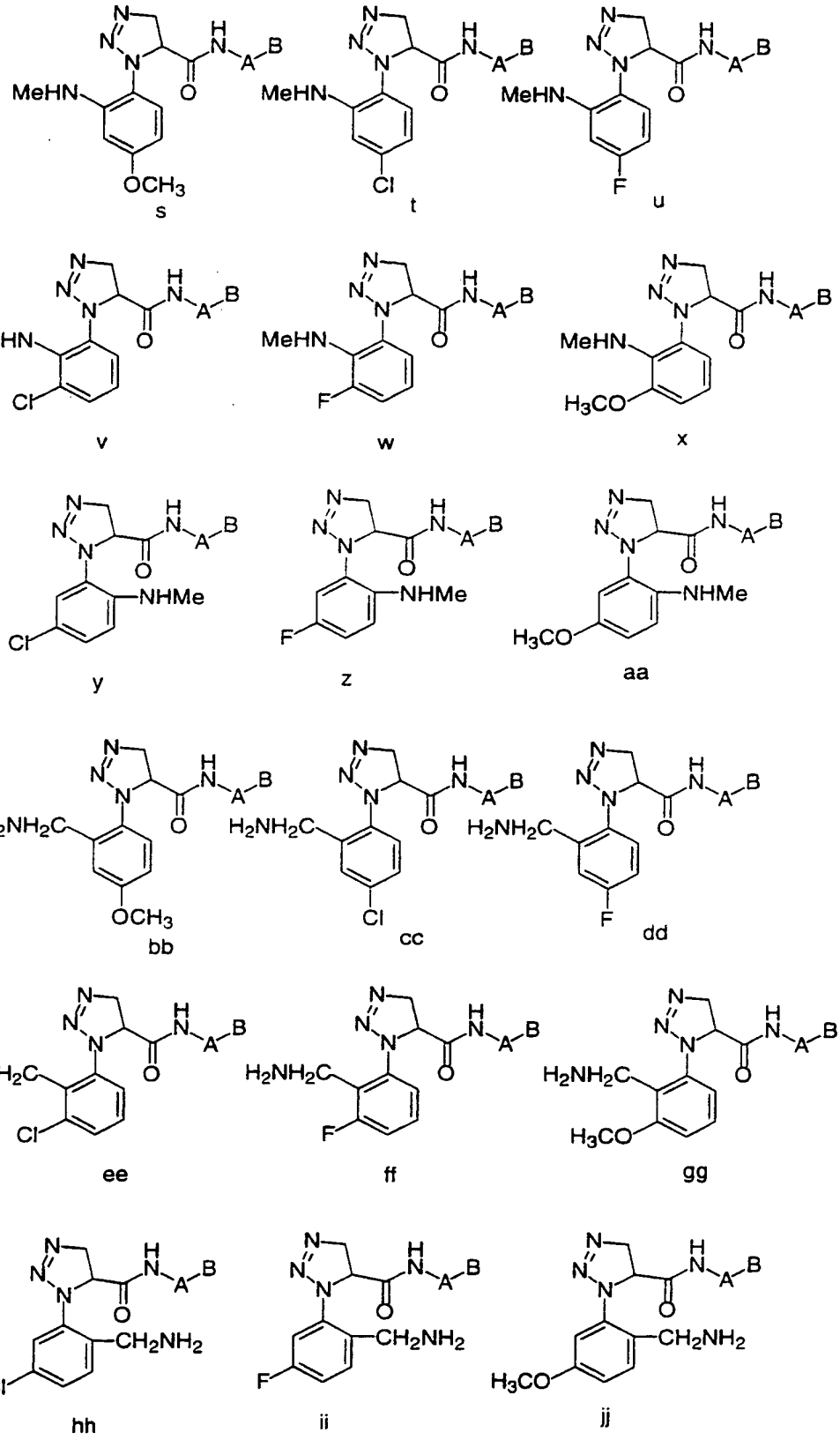
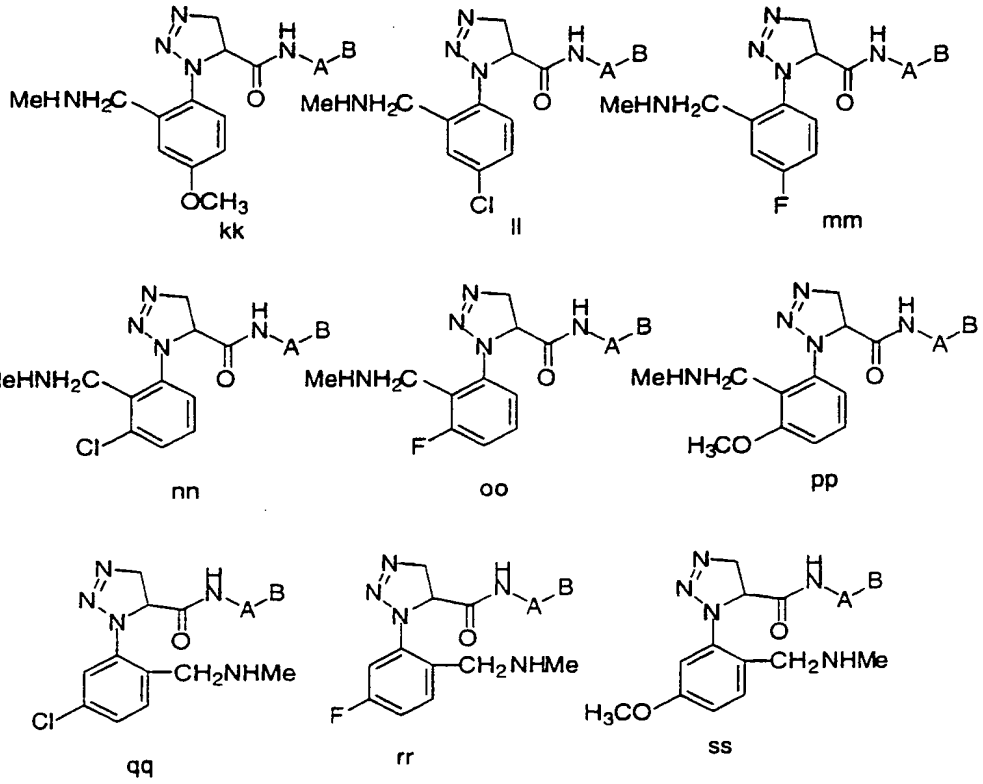




Ex #	A	B
1	phenyl	2-(aminosulfonyl)phenyl
2	phenyl	2-(methylaminosulfonyl)phenyl
3	phenyl	1-pyrrolidinocarbonyl
4	phenyl	2-(methylsulfonyl)phenyl
5	phenyl	4-morpholino
6	phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
7	phenyl	4-morpholinocarbonyl
8	phenyl	2-methyl-1-imidazolyl
9	phenyl	5-methyl-1-imidazolyl
10	phenyl	2-methylsulfonyl-1-imidazolyl
11	2-pyridyl	2-(aminosulfonyl)phenyl
12	2-pyridyl	2-(methylaminosulfonyl)phenyl
13	2-pyridyl	1-pyrrolidinocarbonyl
14	2-pyridyl	2-(methylsulfonyl)phenyl
15	2-pyridyl	4-morpholino
16	2-pyridyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
17	2-pyridyl	4-morpholinocarbonyl

18	2-pyridyl	2-methyl-1-imidazolyl
19	2-pyridyl	5-methyl-1-imidazolyl
20	2-pyridyl	2-methylsulfonyl-1-imidazolyl
21	3-pyridyl	2-(aminosulfonyl)phenyl
22	3-pyridyl	2-(methylaminosulfonyl)phenyl
23	3-pyridyl	1-pyrrolidinocarbonyl
24	3-pyridyl	2-(methylsulfonyl)phenyl
25	3-pyridyl	4-morpholino
26	3-pyridyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
27	3-pyridyl	4-morpholinocarbonyl
28	3-pyridyl	2-methyl-1-imidazolyl
29	3-pyridyl	5-methyl-1-imidazolyl
30	3-pyridyl	2-methylsulfonyl-1-imidazolyl
31	2-pyrimidyl	2-(aminosulfonyl)phenyl
32	2-pyrimidyl	2-(methylaminosulfonyl)phenyl
33	2-pyrimidyl	1-pyrrolidinocarbonyl
34	2-pyrimidyl	2-(methylsulfonyl)phenyl
35	2-pyrimidyl	4-morpholino
36	2-pyrimidyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
37	2-pyrimidyl	4-morpholinocarbonyl
38	2-pyrimidyl	2-methyl-1-imidazolyl
39	2-pyrimidyl	5-methyl-1-imidazolyl
40	2-pyrimidyl	2-methylsulfonyl-1-imidazolyl
41	5-pyrimidyl	2-(aminosulfonyl)phenyl
42	5-pyrimidyl	2-(methylaminosulfonyl)phenyl
43	5-pyrimidyl	1-pyrrolidinocarbonyl
44	5-pyrimidyl	2-(methylsulfonyl)phenyl
45	5-pyrimidyl	4-morpholino
46	5-pyrimidyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
47	5-pyrimidyl	4-morpholinocarbonyl
48	5-pyrimidyl	2-methyl-1-imidazolyl
49	5-pyrimidyl	5-methyl-1-imidazolyl
50	5-pyrimidyl	2-methylsulfonyl-1-imidazolyl
51	2-Cl-phenyl	2-(aminosulfonyl)phenyl
52	2-Cl-phenyl	2-(methylaminosulfonyl)phenyl
53	2-Cl-phenyl	1-pyrrolidinocarbonyl
54	2-Cl-phenyl	2-(methylsulfonyl)phenyl

55	2-Cl-phenyl	4-morpholino
56	2-Cl-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
57	2-Cl-phenyl	4-morpholinocarbonyl
58	2-Cl-phenyl	2-methyl-1-imidazolyl
59	2-Cl-phenyl	5-methyl-1-imidazolyl
60	2-Cl-phenyl	2-methylsulfonyl-1-imidazolyl
61	2-F-phenyl	2-(aminosulfonyl)phenyl
62	2-F-phenyl	2-(methylaminosulfonyl)phenyl
63	2-F-phenyl	1-pyrrolidinocarbonyl
64	2-F-phenyl	2-(methylsulfonyl)phenyl
65	2-F-phenyl	4-morpholino
66	2-F-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
67	2-F-phenyl	4-morpholinocarbonyl
68	2-F-phenyl	2-methyl-1-imidazolyl
69	2-F-phenyl	5-methyl-1-imidazolyl
70	2-F-phenyl	2-methylsulfonyl-1-imidazolyl
71	2,6-diF-phenyl	2-(aminosulfonyl)phenyl
72	2,6-diF-phenyl	2-(methylaminosulfonyl)phenyl
73	2,6-diF-phenyl	1-pyrrolidinocarbonyl
74	2,6-diF-phenyl	2-(methylsulfonyl)phenyl
75	2,6-diF-phenyl	4-morpholino
76	2,6-diF-phenyl	2-(1'-CF_3-tetrazol-2-yl)phenyl
77	2,6-diF-phenyl	4-morpholinocarbonyl
78	2,6-diF-phenyl	2-methyl-1-imidazolyl
79	2,6-diF-phenyl	5-methyl-1-imidazolyl
80	2,6-diF-phenyl	2-methylsulfonyl-1-imidazolyl

Utility

The compounds of this invention are useful as anticoagulants for the treatment or prevention of thromboembolic disorders in mammals. The term "thromboembolic disorders" as used herein includes arterial or venous cardiovascular or cerebrovascular thromboembolic disorders, including, for example, unstable angina, first or recurrent myocardial infarction, ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism,

coronary and cerebral arterial thrombosis, cerebral embolism, kidney embolisms, and pulmonary embolisms. The anticoagulant effect of compounds of the present invention is believed to be due to inhibition of factor Xa or thrombin.

The effectiveness of compounds of the present invention as inhibitors of factor Xa was determined using purified human factor Xa and synthetic substrate. The rate of factor Xa hydrolysis of chromogenic substrate S2222 (Kabi Pharmacia, Franklin, OH) was measured both in the absence and presence of compounds of the present invention. Hydrolysis of the substrate resulted in the release of pNA, which was monitored spectrophotometrically by measuring the increase in absorbance at 405 nM. A decrease in the rate of absorbance change at 405 nm in the presence of inhibitor is indicative of enzyme inhibition. The results of this assay are expressed as inhibitory constant, K_i.

Factor Xa determinations were made in 0.10 M sodium phosphate buffer, pH 7.5, containing 0.20 M NaCl, and 0.5 % PEG 8000. The Michaelis constant, K_m, for substrate hydrolysis was determined at 25°C using the method of Lineweaver and Burk. Values of K_i were determined by allowing 0.2-0.5 nM human factor Xa (Enzyme Research Laboratories, South Bend, IN) to react with the substrate (0.20 mM-1 mM) in the presence of inhibitor. Reactions were allowed to go for 30 minutes and the velocities (rate of absorbance change vs time) were measured in the time frame of 25-30 minutes. The following relationship was used to calculate K_i values:

$$(v_o - v_s)/v_s = I/(K_i\ (1 + S/K_m))$$

where:

v_o is the velocity of the control in the absence of inhibitor;

v_s is the velocity in the presence of inhibitor;

I is the concentration of inhibitor;

K_i is the dissociation constant of the enzyme:inhibitor complex;

S is the concentration of substrate;

K_m is the Michaelis constant.

Using the methodology described above, a compound of the present invention were found to exhibit a K_i of ≤10 μM, thereby confirming the utility of the compounds of the present invention as effective Xa inhibitors.

The antithrombotic effect of compounds of the present invention can be demonstrated in a rabbit arterio-venous (AV) shunt thrombosis model. In this model, rabbits weighing 2-3 kg anesthetized with a mixture of xylazine (10 mg/kg i.m.) and ketamine (50 mg/kg i.m.) are used. A saline-filled AV shunt device is connected between the femoral arterial and the femoral venous cannulae. The AV shunt device consists of a piece of 6-cm tygon tubing which contains a piece of silk thread. Blood will flow from the femoral artery via the AV-shunt into the femoral vein. The exposure of flowing blood to a silk thread will induce the formation of a significant thrombus. After forty minutes, the shunt is disconnected and the silk thread covered with thrombus is weighed. Test agents or vehicle will be given (i.v., i.p., s.c., or orally) prior to the opening of the AV shunt. The percentage inhibition of thrombus formation is determined for each treatment group. The ID50 values (dose which produces 50% inhibition of thrombus formation) are estimated by linear regression.

The compounds of formula (I) may also be useful as inhibitors of serine proteases, notably human thrombin, plasma kallikrein and plasmin. Because of their inhibitory action, these compounds are indicated for use in the prevention or treatment of physiological reactions, blood coagulation and inflammation, catalyzed by the aforesaid class of enzymes. Specifically, the compounds have utility as drugs for the treatment of diseases arising from elevated thrombin activity such as myocardial infarction, and as reagents used as anticoagulants in the processing of blood to plasma for diagnostic and other commercial purposes.

Some compounds of the present invention were shown to be direct acting inhibitors of the serine protease thrombin by their ability to inhibit the cleavage of small molecule substrates by thrombin in a purified system. *In vitro* inhibition constants were determined by the method described

by Kettner et al. in *J. Biol. Chem.* **265**, 18289-18297 (1990), herein incorporated by reference. In these assays, thrombin-mediated hydrolysis of the chromogenic substrate S2238 (Helena Laboratories, Beaumont, TX) was monitored spectrophotometrically. Addition of an inhibitor to the assay mixture results in decreased absorbance and is indicative of thrombin inhibition. Human thrombin (Enzyme Research Laboratories, Inc., South Bend, IN) at a concentration of 0.2 nM in 0.10 M sodium phosphate buffer, pH 7.5, 0.20 M NaCl, and 0.5% PEG 6000, was incubated with various substrate concentrations ranging from 0.20 to 0.02 mM. After 25 to 30 minutes of incubation, thrombin activity was assayed by monitoring the rate of increase in absorbance at 405 nm which arises owing to substrate hydrolysis. Inhibition constants were derived from reciprocal plots of the reaction velocity as a function of substrate concentration using the standard method of Lineweaver and Burk. Using the methodology described above, some compounds of this invention were evaluated and found to exhibit a K_i of less than 10 μm, thereby confirming the utility of the compounds of the present invention as effective thrombin inhibitors.

The compounds of the present invention can be administered alone or in combination with one or more additional therapeutic agents. These include other anti-coagulant or coagulation inhibitory agents, anti-platelet or platelet inhibitory agents, thrombin inhibitors, or thrombolytic or fibrinolytic agents.

The compounds are administered to a mammal in a therapeutically effective amount. By "therapeutically effective amount" it is meant an amount of a compound of Formula I that, when administered alone or in combination with an additional therapeutic agent to a mammal, is effective to prevent or ameliorate the thromboembolic disease condition or the progression of the disease.

By "administered in combination" or "combination therapy" it is meant that the compound of Formula I and one or more additional therapeutic agents are administered concurrently to the mammal being treated. When administered in combination

each component may be administered at the same time or sequentially in any order at different points in time. Thus, each component may be administered separately but sufficiently closely in time so as to provide the desired therapeutic effect. Other anticoagulant agents (or coagulation inhibitory agents) that may be used in combination with the compounds of this invention include warfarin and heparin, as well as other factor Xa inhibitors such as those described in the publications identified above under Background of the Invention.

The term anti-platelet agents (or platelet inhibitory agents), as used herein, denotes agents that inhibit platelet function such as by inhibiting the aggregation, adhesion or granular secretion of platelets. Such agents include, but are not limited to, the various known non-steroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen, sulindac, indomethacin, mefenamate, droxicam, diclofenac, sulfinpyrazone, and piroxicam, including pharmaceutically acceptable salts or prodrugs thereof. Of the NSAIDS, aspirin (acetylsalicyclic acid or ASA), and piroxicam are preferred. Other suitable anti-platelet agents include ticlopidine, including pharmaceutically acceptable salts or prodrugs thereof. Ticlopidine is also a preferred compound since it is known to be gentle on the gastro-intestinal tract in use. Still other suitable platelet inhibitory agents include IIb/IIIa antagonists, thromboxane-A2-receptor antagonists and thromboxane-A2-synthetase inhibitors, as well as pharmaceutically acceptable salts or prodrugs thereof.

The term thrombin inhibitors (or anti-thrombin agents), as used herein, denotes inhibitors of the serine protease thrombin. By inhibiting thrombin, various thrombin-mediated processes, such as thrombin-mediated platelet activation (that is, for example, the aggregation of platelets, and/or the granular secretion of plasminogen activator inhibitor-1 and/or serotonin) and/or fibrin formation are disrupted. A number of thrombin inhibitors are known to one of skill in the art and these inhibitors are contemplated to be used in combination with the present compounds. Such inhibitors include, but are

not limited to, boroarginine derivatives, boropeptides, heparins, hirudin and argatroban, including pharmaceutically acceptable salts and prodrugs thereof. Boroarginine derivatives and boropeptides include N-acetyl and peptide derivatives of boronic acid, such as C-terminal a-aminoboronic acid derivatives of lysine, ornithine, arginine, homoarginine and corresponding isothiouronium analogs thereof. The term hirudin, as used herein, includes suitable derivatives or analogs of hirudin, referred to herein as hirulogs, such as disulfatohirudin. Boropeptide thrombin inhibitors include compounds described in Kettner et al., U.S. Patent No. 5,187,157 and European Patent Application Publication Number 293 881 A2, the disclosures of which are hereby incorporated herein by reference. Other suitable boroarginine derivatives and boropeptide thrombin inhibitors include those disclosed in PCT Application Publication Number 92/07869 and European Patent Application Publication Number 471,651 A2, the disclosures of which are hereby incorporated herein by reference.

The term thrombolytics (or fibrinolytic) agents (or thrombolytics or fibrinolytics), as used herein, denotes agents that lyse blood clots (thrombi). Such agents include tissue plasminogen activator, anistreplase, urokinase or streptokinase, including pharmaceutically acceptable salts or prodrugs thereof. The term anistreplase, as used herein, refers to anisoylated plasminogen streptokinase activator complex, as described, for example, in European Patent Application No. 028,489, the disclosure of which is hereby incorporated herein by reference herein. The term urokinase, as used herein, is intended to denote both dual and single chain urokinase, the latter also being referred to herein as prourokinase.

Administration of the compounds of Formula I of the invention in combination with such additional therapeutic agent, may afford an efficacy advantage over the compounds and agents alone, and may do so while permitting the use of lower doses of each. A lower dosage minimizes the potential of side effects, thereby providing an increased margin of safety.

The compounds of the present invention are also useful as standard or reference compounds, for example as a quality standard or control, in tests or assays involving the inhibition of factor Xa. Such compounds may be provided in a commercial kit, for example, for use in pharmaceutical research involving factor Xa. For example, a compound of the present invention could be used as a reference in an assay to compare its known activity to a compound with an unknown activity. This would ensure the experimenter that the assay was being performed properly and provide a basis for comparison, especially if the test compound was a derivative of the reference compound. When developing new assays or protocols, compounds according to the present invention could be used to test their effectiveness.

The compounds of the present invention may also be used in diagnostic assays involving factor Xa. For example, the presence of factor Xa in an unknown sample could be determined by addition of chromogenic substrate S2222 to a series of solutions containing test sample and optionally one of the compounds of the present invention. If production of pNA is observed in the solutions containing test sample, but not in the presence of a compound of the present invention, then one would conclude factor Xa was present.

Dosage and Formulation

The compounds of this invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. They may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. They can be administered alone, but generally will be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient,and the effect desired. A physician or veterinarian can determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the thromboembolic disorder.

By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to 1000 mg/kg of body weight, preferably between about 0.01 to 100 mg/kg of body weight per day, and most preferably between about 1.0 to 20 mg/kg/day. Intravenously, the most preferred doses will range from about 1 to about 10 mg/kg/minute during a constant rate infusion. Compounds of this invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

Compounds of this invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal skin patches. When administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

The compounds are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as pharmaceutical carriers) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined

with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl callulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

Compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans,

polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels.

Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 100 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field.

Representative useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

A large number of unit capsules can be prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestable oil such as soybean oil, cottonseed oil or olive oil may be prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules should be washed and dried.

Tablets

Tablets may be prepared by conventional procedures so that the dosage unit is 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Injectable

A parenteral composition suitable for administration by injection may be prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution should be made isotonic with sodium chloride and sterilized.

Suspension

An aqueous suspension can be prepared for oral administration so that each 5 mL contain 100 mg of finely divided active ingredient, 200 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 mL of vanillin.

Where the compounds of this invention are combined with other anticoagulant agents, for example, a daily dosage may be

about 0.1 to 100 milligrams of the compound of Formula I and about 1 to 7.5 milligrams of the second anticoagulant, per kilogram of patient body weight. For a tablet dosage form, the compounds of this invention generally may be present in an amount of about 5 to 10 milligrams per dosage unit, and the second anti-coagulant in an amount of about 1 to 5 milligrams per dosage unit.

Where the compounds of Formula I are administered in combination with an anti-platelet agent, by way of general guidance, typically a daily dosage may be about 0.01 to 25 milligrams of the compound of Formula I and about 50 to 150 milligrams of the anti-platelet agent, preferably about 0.1 to 1 milligrams of the compound of Formula I and about 1 to 3 milligrams of antiplatelet agents, per kilogram of patient body weight.

Where the compounds of Formula I are adminstered in combination with thrombolytic agent, typically a daily dosage may be about 0.1 to 1 milligrams of the compound of Formula I, per kilogram of patient body weight and, in the case of the thrombolytic agents, the usual dosage of the thrombolyic agent when administered alone may be reduced by about 70-80% when administered with a compound of Formula I.

Where two or more of the foregoing second therapeutic agents are administered with the compound of Formula I, generally the amount of each component in a typical daily dosage and typical dosage form may be reduced relative to the usual dosage of the agent when administered alone, in view of the additive or synergistic effect of the therapeutic agents when administered in combination.

Particularly when provided as a single dosage unit, the potential exists for a chemical interaction between the combined active ingredients. For this reason, when the compound of Formula I and a second therapeutic agent are combined in a single dosage unit they are formulated such that although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized (that is, reduced). For example, one active ingredient may be enteric coated. By enteric coating

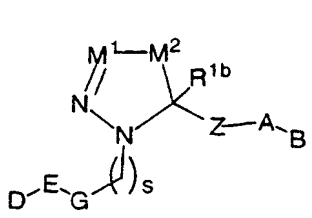
one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines. One of the active ingredients may also be coated with a material which effects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a lowviscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the same manner, will be readily apparent to those skilled in the art, once armed with the present disclosure.

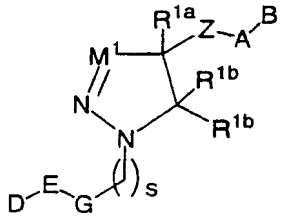
Obviously, numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced otherwise that as specifically described herein.

WHAT IS CLAIMED IS:

1. A compound of formula I:



I



II

or a stereoisomer or pharmaceutically acceptable salt thereof, wherein;

M^1 is N or CR^{1c};

M^2 is NR^{1a} or $CR^{1a}R^{1a}$, provided that only one of M^1 and M^2 is a N atom;

D is selected from $C(=NR^8)NR^7R^9$, $NHC(=NR^8)NR^7R^9$, $NR^8CH(=NR^7)$, $C(O)NR^7R^8$, and $CR^8R^9NR^7R^8$;

E is selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, and piperidinyl substituted with 1 R;

alternatively, D-E-G together represent pyridyl substituted with 1 R;

R is selected from H, Cl, F, Br, I, $(CH_2)_tOR^3$, C_{1-4} alkyl, OCF_3, CF_3, $C(O)NR^7R^8$, and $(CR^8R^9)_tNR^7R^8$;

G is selected from $NHCH_2$, OCH_2, and SCH_2, provided that when s is 0, then G is absent;

Z is selected from a C_{1-4} alkylene, $(CH_2)_rO(CH_2)_r$, $(CH_2)_rNR^3(CH_2)_r$, $(CH_2)_rC(O)(CH_2)_r$, $(CH_2)_rC(O)O(CH_2)_r$, $(CH_2)_rOC(O)(CH_2)_r$, $(CH_2)_rC(O)NR^3(CH_2)_r$, $(CH_2)_rNR^3C(O)(CH_2)_r$, $(CH_2)_rOC(O)O(CH_2)_r$, $(CH_2)_rOC(O)NR^3(CH_2)_r$, $(CH_2)_rNR^3C(O)O(CH_2)_r$,

$(CH_2)_rNR^3C(O)NR^3(CH_2)_r$, $(CH_2)_rS(O)_p(CH_2)_r$, $(CH_2)_rSO_2NR^3(CH_2)_r$, $(CH_2)_rNR^3SO_2(CH_2)_r$, and $(CH_2)_rNR^3SO_2NR^3(CH_2)_r$, provided that Z does not form a N-N, N-O, N-S, NCH_2N, NCH_2O, or NCH_2S bond with group A;

R^{1a} and R^{1b} are, at each occurrence, independently selected from H, $-(CH_2)_r-R^{1'}$, $NCH_2R^{1''}$, $OCH_2R^{1''}$, $SCH_2R^{1''}$, $N(CH_2)_2(CH_2)_tR^{1'}$, $O(CH_2)_2(CH_2)_tR^{1'}$, and $S(CH_2)_2(CH_2)_tR^{1'}$;

R^{1c} is selected from H, $-(CH_2)_q-R^{1'}$, C_{1-3} alkyl, $C(O)R^{2c}$, $(CF_2)_rCO_2R^{2c}$, $C(O)NR^2R^{2a}$, C_{3-6} carbocyclic residue substituted with 0-2 R^4, and 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^4;

$R^{1'}$ is selected from H, C_{1-3} alkyl, halo, $(CF_2)_rCF_3$, OR^2, NR^2R^{2a}, $C(O)R^{2c}$, $OC(O)R^2$, $(CF_2)_rCO_2R^{2c}$, $S(O)_pR^{2b}$, $NR^2(CH_2)_rOR^2$, $NR^2C(O)R^{2b}$, $NR^2C(O)NHR^{2b}$, $NR^2C(O)_2R^{2a}$, $OC(O)NR^{2b}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2R^{2b}$, C_{3-6} carbocyclic residue substituted with 0-2 R^4, and 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^4;

$R^{1''}$ is selected from H, $C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $S(O)R^{2b}$, $S(O)_2R^{2b}$, and $SO_2NR^2R^{2a}$;

R^2, at each occurrence, is selected from H, CF_3, C_{1-6} alkyl, benzyl, C_{3-6} carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

R^{2a}, at each occurrence, is selected from H, CF_3, C_{1-6} alkyl, benzyl, C_{3-6} carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

R^{2b}, at each occurrence, is selected from CF_3, C_{1-4} alkoxy, C_{1-6} alkyl, benzyl, C_{3-6} carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

R^{2c}, at each occurrence, is selected from CF_3, OH, C_{1-4} alkoxy, C_{1-6} alkyl, benzyl, C_{3-6} carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

alternatively, R^2 and R^{2a} combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring substituted with 0-2 R^{4b} which contains from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

R^3, at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

R^{3a}, at each occurrence, is selected from H, C_{1-4} alkyl, and phenyl;

A is selected from:

C_{3-10} carbocyclic residue substituted with 0-2 R^4, and

5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^4;

B is selected from:

X-Y, NR^2R^{2a}, $C(=NR^2)NR^2R^{2a}$, $NR^2C(=NR^2)NR^2R^{2a}$,

C_{3-10} carbocyclic residue substituted with 0-2 R^{4a}, and

5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a};

X is selected from C_{1-4} alkylene, $-CR^2(CR^2R^{2b})(CH_2)_t-$, $-C(O)-$, $-C(=NR)-$, $-CR^2(NR^{1''}R^2)-$, $-CR^2(OR^2)-$, $-CR^2(SR^2)-$, $-C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)$, $-S(O)_p-$, $-S(O)_pCR^2R^{2a}-$, $-CR^2R^{2a}S(O)_p-$, $-S(O)_2NR^2-$, $-NR^2S(O)_2-$, $-NR^2S(O)_2CR^2R^{2a}-$, $-CR^2R^{2a}S(O)_2NR^2-$, $-NR^2S(O)_2NR^2-$, $-C(O)NR^2-$, $-NR^2C(O)-$, $-C(O)NR^2CR^2R^{2a}-$, $-NR^2C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)NR^2-$, $-CR^2R^{2a}NR^2C(O)-$, $-NR^2C(O)O-$, $-OC(O)NR^2-$, $-NR^2C(O)NR^2-$, $-NR^2-$, $-NR^2CR^2R^{2a}-$, $-CR^2R^{2a}NR^2-$, O, $-CR^2R^{2a}O-$, and $-OCR^2R^{2a}-$;

Y is selected from:

$(CH_2)_rNR^2R^{2a}$, provided that X-Y do not form a N-N, O-N, or S-N bond,

C_{3-10} carbocyclic residue substituted with 0-2 R^{4a}, and

5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a};

R^4, at each occurrence, is selected from =O, $(CH_2)_rOR^2$, halo, C_{1-4} alkyl, -CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2b}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $CH(=NR^2)NR^2R^{2a}$, $NHC(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, $NR^2SO_2-C_{1-4}$ alkyl, $NR^2SO_2R^5$, $S(O)_pR^5$, $(CF_2)_rCF_3$, $NCH_2R^{1''}$, $OCH_2R^{1''}$, $SCH_2R^{1''}$, $N(CH_2)_2(CH_2)_tR^{1'}$, $O(CH_2)_2(CH_2)_tR^{1'}$, and $S(CH_2)_2(CH_2)_tR^{1'}$,

alternatively, one R^4 is a 5-6 membered aromatic heterocycle containing from 1-4 heteroatoms selected from the group consisting of N, O, and S;

R^{4a}, at each occurrence, is selected from =O, $(CH_2)_rOR^2$, halo, C_{1-4} alkyl, -CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2b}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $CH(=NR^2)NR^2R^{2a}$, $NHC(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, $NR^2SO_2-C_{1-4}$ alkyl, $NR^2SO_2R^5$, $S(O)_pR^5$, and $(CF_2)_rCF_3$;

alternatively, one R^{4a} is a 5-6 membered aromatic heterocycle containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-1 R^5;

R^{4b}, at each occurrence, is selected from =O, $(CH_2)_rOR^3$, halo, C_{1-4} alkyl, -CN, NO_2, $(CH_2)_rNR^3R^{3a}$, $(CH_2)_rC(O)R^3$, $NR^3C(O)R^{3a}$, $C(O)NR^3R^{3a}$, $NR^3C(O)NR^3R^{3a}$, $CH(=NR^3)NR^3R^{3a}$, $NH^3C(=NR^3)NR^3R^{3a}$, $SO_2NR^3R^{3a}$, $NR^3SO_2NR^3R^{3a}$, NR^3SO_2-C_{1-4} alkyl, $NR^3SO_2CF_3$, NR^3SO_2-phenyl, $S(O)_pCF_3$, $S(O)_p$-C_{1-4} alkyl, $S(O)_p$-phenyl, and $(CF_2)_rCF_3$;

R^5, at each occurrence, is selected from CF_3, C_{1-6} alkyl, phenyl substituted with 0-2 R^6, and benzyl substituted with 0-2 R^6;

R^6, at each occurrence, is selected from H, OH, $(CH_2)_rOR^2$, halo, C_{1-4} alkyl, CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2b}$, $NR^2C(O)R^{2b}$, $NR^2C(O)NR^2R^{2a}$, $CH(=NH)NH_2$, $NHC(=NH)NH_2$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, and $NR^2SO_2C_{1-4}$ alkyl;

R^7, at each occurrence, is selected from H, OH, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxy, C_{1-4} alkoxycarbonyl, $(CH_2)_n$-phenyl, C_{6-10} aryloxy, C_{6-10} aryloxycarbonyl, C_{6-10} arylmethylcarbonyl, C_{1-4} alkylcarbonyloxy C_{1-4} alkoxycarbonyl, C_{6-10} arylcarbonyloxy C_{1-4} alkoxycarbonyl, C_{1-6} alkylaminocarbonyl, phenylaminocarbonyl, and phenyl C_{1-4} alkoxycarbonyl;

R^8, at each occurrence, is selected from H, C_{1-6} alkyl and $(CH_2)_n$-phenyl;

alternatively, R^7 and R^8 combine to form a 5 or 6 membered saturated, ring which contains from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

R^9, at each occurrence, is selected from H, C_{1-6} alkyl and $(CH_2)_n$-phenyl;

n, at each occurrence, is selected from 0, 1, 2, and 3;

m, at each occurrence, is selected from 0, 1, and 2;

p, at each occurrence, is selected from 0, 1, and 2;

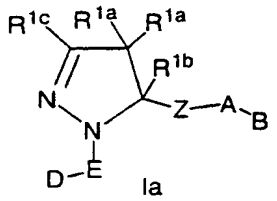
q, at each occurrence is selected from 1 and 2;

r, at each occurrence, is selected from 0, 1, 2, and 3;

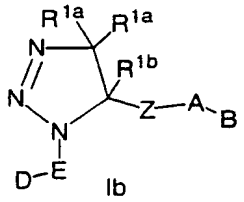
s, at each occurrence, is selected from 0, 1, and 2; and,

t, at each occurrence, is selected from 0 and 1.

2. A compound according to Claim 1, wherein the compound is of formula Ia or Ib:



Ia



Ib

wherein;

Z is selected from a CH_2O, OCH_2, CH_2NH, $NHCH_2$, $C(O)$, $CH_2C(O)$, $C(O)CH_2$, $NHC(O)$, $C(O)NH$, $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH, and $NHSO_2$, provided that Z does not form a N-N, N-O, NCH_2N, or NCH_2O bond with group A;

A is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^4;

phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl,

1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, benzofuranyl, benzothiofuranyl, indolyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, and isoindazolyl;

B is selected from: Y, X-Y, NR^2R^{2a}, $C(=NR^2)NR^2R^{2a}$, and $NR^2C(=NR^2)NR^2R^{2a}$;

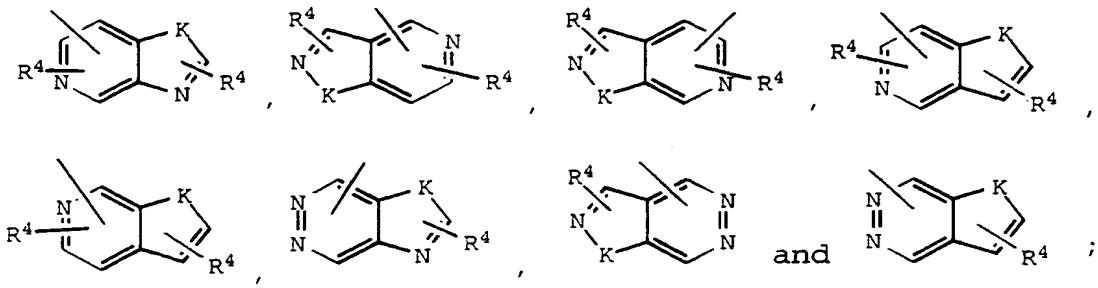
X is selected from C_{1-4} alkylene, -C(O)-, -C(=NR)-, $-CR^2(NR^2R^{2a})-$, $-C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)$, $-C(O)NR^2-$, $-NR^2C(O)-$, $-C(O)NR^2CR^2R^{2a}-$, $-NR^2C(O)CR^2R^{2a}-$, $-CR^2R^{2a}C(O)NR^2-$, $-CR^2R^{2a}NR^2C(O)-$, $-NR^2C(O)NR^2-$, $-NR^2-$, $-NR^2CR^2R^{2a}-$, $-CR^2R^{2a}NR^2-$, O, $-CR^2R^{2a}O-$, and $-OCR^2R^{2a}-$;

Y is NR^2R^{2a}, provided that X-Y do not form a N-N or O-N bond;

alternatively, Y is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^{4a};

cylcopropyl, cyclopentyl, cyclohexyl, phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, isoxazolinyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, benzofuranyl, benzothiofuranyl, indolyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, and isoindazolyl;

alternatively, Y is selected from the following bicyclic heteroaryl ring systems:



K is selected from O, S, NH, and N.

3. A compound according to Claim 2, wherein;

Z is selected from a C(O), $CH_2C(O)$, $C(O)CH_2$, NHC(O), C(O)NH, $C(O)N(CH_3)$, $CH_2S(O)_2$, $S(O)_2(CH_2)$, SO_2NH, and $NHSO_2$, provided that Z does not form a N-N or NCH_2N bond with group A.

4. A compound according to Claim 3, wherein;

E is phenyl substituted with R or 2-pyridyl substituted with R;

D is selected from $C(O)NH_2$, $C(=NH)NH_2$, CH_2NH_2, CH_2NHCH_3, $CH(CH_3)NH_2$, and $C(CH_3)_2NH_2$; and,

R is selected from H, OCH_3, Cl, and F.

5. A compound according to Claim 4, wherein;

D-E is selected from 3-amidinophenyl, 3-aminomethylphenyl, 3-aminocarbonylphenyl, 3-(methylaminomethyl)phenyl, 3-(1-aminoethyl)phenyl, 3-(2-amino-2-propyl)phenyl, 4-chloro-3-amidinophenyl, 4-chloro-3-aminomethylphenyl, 4-chloro-3-(methylaminomethyl)phenyl, 4-fluoro-3-amidinophenyl, 4-fluoro-3-aminomethylphenyl, 4-fluoro-3-

(methylaminomethyl)phenyl, 6-amidinopyrid-2-yl, 6-aminomethylpyrid-2-yl, 6-aminocarbonylpyrid-2-yl, 6-(methylaminomethyl)pyrid-2-yl, 6-(1-aminoethyl)pyrid-2-yl, and 6-(2-amino-2-propyl)pyrid-2-yl.

6. A compound according to Claim 3, wherein;

Z is $C(O)CH_2$ and CONH, provided that Z does not form a N-N bond with group A;

A is selected from phenyl, pyridyl, and pyrimidyl, and is substituted with 0-2 R^4; and,

B is selected from X-Y, phenyl, pyrrolidino, morpholino, 1,2,3-triazolyl, and imidazolyl, and is substituted with 0-1 R^{4a};

R^4, at each occurrence, is selected from OH, $(CH_2)_rOR^2$, halo, C_{1-4} alkyl, $(CH_2)_rNR^2R^{2a}$, and $(CF_2)_rCF_3$;

R^{4a} is selected from C_{1-4} alkyl, CF_3, $S(O)_pR^5$, $SO_2NR^2R^{2a}$, and 1-CF_3-tetrazol-2-yl;

R^5, at each occurrence, is selected from CF_3, C_{1-6} alkyl, phenyl, and benzyl;

X is CH_2 or C(O); and,

Y is selected from pyrrolidino and morpholino.

7. A compound according to Claim 6, wherein;

A is selected from the group: phenyl, 2-pyridyl, 3-pyridyl, 2-pyrimidyl, 2-Cl-phenyl, 3-Cl-phenyl, 2-F-phenyl, 3-F-phenyl, 2-methylphenyl, 2-aminophenyl, and 2-methoxyphenyl; and,

B is selected from the group: 2-CF_3-phenyl, 2-(aminosulfonyl)phenyl, 2-(methylaminosulfonyl)phenyl, 2-(dimethylaminosulfonyl)phenyl, 1-pyrrolidinocarbonyl, 2-(methylsulfonyl)phenyl, 4-morpholino, 2-(1'-CF_3-tetrazol-2-yl)phenyl, 4-morpholinocarbonyl, 2-methyl-1-imidazolyl, 5-methyl-1-imidazolyl, 2-methylsulfonyl-1-imidazolyl and, 5-methyl-1,2,3-triazolyl.

8. A compound according to Claim 3, wherein;

E is phenyl substituted with R or 2-pyridyl substituted with R;

D is selected from $C(O)NH_2$, $C(=NH)NH_2$, CH_2NH_2, CH_2NHCH_3, $CH(CH_3)NH_2$, and $C(CH_3)_2NH_2$; and,

R is selected from H, OCH_3, Cl, and F;

Z is $C(O)CH_2$ and CONH, provided that Z does not form a N-N bond with group A;

A is selected from phenyl, pyridyl, and pyrimidyl, and is substituted with 0-2 R^4; and,

B is selected from X-Y, phenyl, pyrrolidino, morpholino, 1,2,3-triazolyl, and imidazolyl, and is substituted with 0-1 R^{4a};

R^4, at each occurrence, is selected from OH, $(CH_2)_rOR^2$, halo, C_{1-4} alkyl, $(CH_2)_rNR^2R^{2a}$, and $(CF_2)_rCF_3$;

R^{4a} is selected from C_{1-4} alkyl, CF_3, $S(O)_pR^5$, $SO_2NR^2R^{2a}$, and 1-CF_3-tetrazol-2-yl;

R^5, at each occurrence, is selected from CF_3, C_{1-6} alkyl, phenyl, and benzyl;

X is CH_2 or C(O); and,

Y is selected from pyrrolidino and morpholino.

9. A compound according to Claim 8 wherein;

D-E is selected from 3-amidinophenyl, 3-aminomethylphenyl, 3-aminocarbonylphenyl, 3-(methylaminomethyl)phenyl, 3-(1-aminoethyl)phenyl, 3-(2-amino-2-propyl)phenyl, 4-chloro-3-amidinophenyl, 4-chloro-3-aminomethylphenyl, 4-chloro-3-(methylaminomethyl)phenyl, 4-fluoro-3-amidinophenyl, 4-fluoro-3-aminomethylphenyl, 4-fluoro-3-(methylaminomethyl)phenyl, 6-amidinopyrid-2-yl, 6-aminomethylpyrid-2-yl, 6-aminocarbonylpyrid-2-yl, 6-(methylaminomethyl)pyrid-2-yl, 6-(1-aminoethyl)pyrid-2-yl, 6-(2-amino-2-propyl)pyrid-2-yl;

A is selected from the group: phenyl, 2-pyridyl, 3-pyridyl, 2-pyrimidyl, 2-Cl-phenyl, 3-Cl-phenyl, 2-F-phenyl, 3-F-phenyl, 2-methylphenyl, 2-aminophenyl, and 2-methoxyphenyl; and,

B is selected from the group: 2-CF_3-phenyl, 2-(aminosulfonyl)phenyl, 2-(methylaminosulfonyl)phenyl, 2-(dimethylaminosulfonyl)phenyl, 1-pyrrolidinocarbonyl, 2-(methylsulfonyl)phenyl, 4-morpholino, 2-(1'-CF_3-tetrazol-2-yl)phenyl, 4-morpholinocarbonyl, 2-methyl-1-imidazolyl, 5-methyl-1-imidazolyl, 2-methylsulfonyl-1-imidazolyl and, 5-methyl-1,2,3-triazolyl.

10. A compound according to Claim 9, wherein the compound is of formula Ia.

11. A compound according to Claim 9, wherein the compound is of formula Ib.

12. A compound according to Claim 3, wherein;

D is selected from $C(=NR^8)NR^7R^9$, $C(O)NR^7R^8$, NR^7R^8, and $CH_2NR^7R^8$;

E is phenyl substituted with R or pyridyl substituted with R;

R is selected from H, Cl, F, OR^3, CH_3, CH_2CH_3, OCF_3, and CF_3;

Z is selected from C(O), $CH_2C(O)$, $C(O)CH_2$, NHC(O), and C(O)NH, provided that Z does not form a N-N bond with group A;

R^{1a} and R^{1b} are, at each occurrence, independently selected from H, $-(CH_2)_r-R^{1'}$, $NCH_2R^{1''}$, $OCH_2R^{1''}$, $SCH_2R^{1''}$, $N(CH_2)_2(CH_2)_tR^{1'}$, $O(CH_2)_2(CH_2)_tR^{1'}$, and $S(CH_2)_2(CH_2)_tR^{1'}$;

R^{1c} is selected from H, $-(CH_2)_q-R^{1'}$, C_{1-3} alkyl, $C(O)R^{2c}$, $(CF_2)_rCO_2R^{2c}$, and $C(O)NR^2R^{2a}$;

$R^{1'}$, at each occurrence, is selected from H, C_{1-3} alkyl, halo, $(CF_2)_rCF_3$, OR^2, NR^2R^{2a}, $C(O)R^{2c}$, $(CF_2)_rCO_2R^{2c}$, $S(O)_pR^{2b}$, $NR^2(CH_2)_rOR^2$, $NR^2C(O)R^{2b}$, $NR^2C(O)_2R^{2b}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, and $NR^2SO_2R^{2b}$;

A is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^4;

phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, and imidazolyl;

B is selected from: Y, X-Y, NR^2R^{2a}, $C(=NR^2)NR^2R^{2a}$, and $NR^2C(=NR^2)NR^2R^{2a}$;

X is selected from CH_2, $-CR^2(CR^2R^{2b})(CH_2)_t-$, $-C(O)-$, $-C(=NR)-$, $-CH(NR^2R^{2a})-$, $-C(O)NR^2-$, $-NR^2C(O)-$, $-NR^2C(O)NR^2-$, $-NR^2-$, and O;

Y is NR^2R^{2a}, provided that X-Y do not form a N-N or O-N bond;

alternatively, Y is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^{4a};

phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, isoxazolinyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, and 1,3,4-triazolyl;

R^4, at each occurrence, is selected from =O, OH, Cl, F, C_{1-4} alkyl, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2b}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $CH(=NH)NH_2$, $NHC(=NH)NH_2$, $SO_2NR^2R^{2a}$, NR^2SO_2-C_{1-4} alkyl, $NR^2SO_2R^5$, $S(O)_pR^5$, and $(CF_2)_rCF_3$;

R^{4a}, at each occurrence, is selected from =O, OH, Cl, F, C_{1-4} alkyl, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2b}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $CH(=NH)NH_2$, $NHC(=NH)NH_2$, $SO_2NR^2R^{2a}$, NR^2SO_2-C_{1-4} alkyl, $NR^2SO_2R^5$, $S(O)_pR^5$, $(CF_2)_rCF_3$, and 1-CF_3-tetrazol-2-yl;

R^5, at each occurrence, is selected from CF_3, C_{1-6} alkyl, phenyl substituted with 0-2 R^6, and benzyl substituted with 0-2 R^6;

R^6, at each occurrence, is selected from H, =O, OH, OR^2, Cl, F, CH_3, CN, NO_2, $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2b}$, $NR^2C(O)R^{2b}$, $CH(=NH)NH_2$, $NHC(=NH)NH_2$, and $SO_2NR^2R^{2a}$;

R^7, at each occurrence, is selected from H, OH, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxy, C_{1-4} alkoxycarbonyl, benzyl, C_{6-10} aryloxy, C_{6-10} aryloxycarbonyl, C_{6-10} arylmethylcarbonyl, C_{1-4} alkylcarbonyloxy C_{1-4} alkoxycarbonyl, C_{6-10} arylcarbonyloxy C_{1-4} alkoxycarbonyl, C_{1-6} alkylaminocarbonyl, phenylaminocarbonyl, and phenyl C_{1-4} alkoxycarbonyl;

R^8, at each occurrence, is selected from H, C_{1-6} alkyl and benzyl; and

alternatively, R^7 and R^8 combine to form a morpholino group; and,

R^9, at each occurrence, is selected from H, C_{1-6} alkyl and benzyl.

13. A compound according to Claim 12, wherein;

E is phenyl substituted with R or 2-pyridyl substituted with R;

R is selected from H, Cl, F, OCH_3, CH_3, OCF_3, and CF_3;

Z is selected from a $C(O)CH_2$ and C(O)NH, provided that Z does not form a N-N bond with group A;

R^{1a}, at each occurrence, is selected from H, CH_3, CH_2CH_3, Cl, F, CF_3, OCH_3, NR^2R^{2a}, $S(O)_pR^{2b}$, $CH_2S(O)_pR^{2b}$, $CH_2NR^2S(O)_pR^{2b}$, $C(O)R^{2c}$, $CH_2C(O)R^{2c}$, $C(O)NR^2R^{2a}$, and $SO_2NR^2R^{2a}$;

R^{1b} is selected from H, CH_3, CH_2CH_3, Cl, F, CF_3, OCH_3, NR^2R^{2a}, $S(O)_pR^{2b}$, $CH_2S(O)_pR^{2b}$, $CH_2NR^2S(O)_pR^{2b}$, $C(O)R^{2c}$, $CH_2C(O)R^{2c}$, $C(O)NR^2R^{2a}$, and $SO_2NR^2R^{2a}$;

R^{1c} is selected from H, CH_3, CH_2CH_3, CF_3, $CH_2S(O)_pR^{2b}$, $CH_2NR^2S(O)_pR^{2b}$, $C(O)R^{2c}$, $CH_2C(O)R^{2c}$, and $C(O)NR^2R^{2a}$;

A is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^4;

phenyl, pyridyl, pyrimidyl, furanyl, thiophenyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, and imidazolyl;

B is selected from: Y and X-Y;

X is selected from CH_2, $-CR^2(CR^2R^{2b})-$, $-C(O)-$, $-C(=NR)-$, $-CH(NR^2R^{2a})-$, $-C(O)NR^2-$, $-NR^2C(O)-$, $-NR^2C(O)NR^2-$, $-NR^2-$, and O;

Y is NR^2R^{2a}, provided that X-Y do not form a N-N or O-N bond;

alternatively, Y is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^{4a};

phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, isoxazolinyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, and 1,3,4-triazolyl;

R^2, at each occurrence, is selected from H, CF_3, CH_3, benzyl, and phenyl;

R^{2a}, at each occurrence, is selected from H, CF_3, CH_3, benzyl, and phenyl;

R^{2b}, at each occurrence, is selected from CF_3, OCH_3, CH_3, benzyl, and phenyl;

R^{2c}, at each occurrence, is selected from CF_3, OH, OCH_3, CH_3, benzyl, and phenyl;

alternatively, R^2 and R^{2a} combine to form a 5 or 6 membered saturated, partially unsaturated, or unsaturated ring which contains from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

R^3, at each occurrence, is selected from H, CH_3, CH_2CH_3, and phenyl;

R^{3a}, at each occurrence, is selected from H, CH_3, CH_2CH_3, and phenyl;

R^4, at each occurrence, is selected from OH, Cl, F, CH_3, CH_2CH_3, NR^2R^{2a}, $CH_2NR^2R^{2a}$, $C(O)R^{2b}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, and CF_3;

R^{4a}, at each occurrence, is selected from OH, Cl, F, CH_3, CH_2CH_3, NR^2R^{2a}, $CH_2NR^2R^{2a}$, $C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $S(O)_pR^5$, CF_3, and 1-CF_3-tetrazol-2-yl;

R^5, at each occurrence, is selected from CF_3, C_{1-6} alkyl, phenyl substituted with 0-2 R^6, and benzyl substituted with 1 R^6;

R^6, at each occurrence, is selected from H, OH, OCH_3, Cl, F, CH_3, CN, NO_2, NR^2R^{2a}, $CH_2NR^2R^{2a}$, and $SO_2NR^2R^{2a}$;

R^7, at each occurrence, is selected from H, OH, C_{1-3} alkyl, C_{1-3} alkylcarbonyl, C_{1-3} alkoxy, C_{1-4} alkoxycarbonyl, benzyl, phenoxy, phenoxycarbonyl, benzylcarbonyl, C_{1-4} alkylcarbonyloxy C_{1-4} alkoxycarbonyl, phenylcarbonyloxy C_{1-4} alkoxycarbonyl, C_{1-6} alkylaminocarbonyl, phenylaminocarbonyl, and phenyl C_{1-4} alkoxycarbonyl;

R^8, at each occurrence, is selected from H, CH_3, and benzyl; and,

alternatively, R^7 and R^8 combine to form a morpholino group;

R^9, at each occurrence, is selected from H, CH_3, and benzyl.

14. A compound according to Claim 13, wherein;

R^{1a}, at each occurrence, is selected from H, CH_3, CH_2CH_3, Cl, F, CF_3, OCH_3, NR^2R^{2a}, $S(O)_pR^{2b}$, $C(O)NR^2R^{2a}$, $CH_2S(O)_pR^{2b}$, $CH_2NR^2S(O)_pR^{2b}$, $C(O)R^{2c}$, $CH_2C(O)R^{2c}$, and $SO_2NR^2R^{2a}$;

R^{1b} is selected from H, CH_3, CH_2CH_3, Cl, F, CF_3, OCH_3, NR^2R^{2a}, $S(O)_pR^{2b}$, $C(O)NR^2R^{2a}$, $CH_2S(O)_pR^{2b}$, $CH_2NR^2S(O)_pR^{2b}$, $C(O)R^{2b}$, $CH_2C(O)R^{2b}$, and $SO_2NR^2R^{2a}$;

R^{1c} is selected from H, CH_3, CH_2CH_3, CF_3, $C(O)NR^2R^{2a}$, $CH_2S(O)_pR^{2b}$, $CH_2NR^2S(O)_pR^{2b}$, $C(O)R^{2b}$, and $CH_2C(O)R^{2b}$;

A is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^4;

phenyl, pyridyl, and pyrimidyl;

B is selected from: Y and X-Y;

X is selected from -C(O)- and O;

Y is NR^2R^{2a}, provided that X-Y do not form a O-N bond;

alternatively, Y is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^{4a};

phenyl, piperazinyl, pyridyl, pyrimidyl, morpholinyl, pyrrolidinyl, imidazolyl, and 1,2,3-triazolyl;

R^2, at each occurrence, is selected from H, CF_3, CH_3, benzyl, and phenyl;

R^{2a}, at each occurrence, is selected from H, CF_3, CH_3, benzyl, and phenyl;

R^{2b}, at each occurrence, is selected from CF_3, OCH_3, CH_3, benzyl, and phenyl;

R^{2c}, at each occurrence, is selected from CF_3, OH, OCH_3, CH_3, benzyl, and phenyl;

alternatively, R^2 and R^{2a} combine to form a ring system selected from pyrrolidinyl, piperazinyl and morpholino;

R^4, at each occurrence, is selected from Cl, F, CH_3, NR^2R^{2a}, and CF_3;

R^{4a}, at each occurrence, is selected from Cl, F, CH_3, $SO_2NR^2R^{2a}$, $S(O)_pR^5$, and CF_3; and,

R^5, at each occurrence, is selected from CF_3 and CH_3.

15. A compound according to Claim 1, wherein the compound is selected from the group:

1-(3-amidinophenyl)-5-[[(2'-methylsulfonyl-[1,1']-biphen-4-yl)-aminocarbonyl]-3-trifluoromethyl-pyrazoline; and,

1-(3-aminomethylphenyl)-5-[[(2'-methylsulfonyl-[1,1']-biphen-4-yl)-aminocarbonyl]-3-trifluoromethyl-pyrazoline;

and pharmaceutically acceptable salts thereof.

16. A pharmaceutical composition, comprising: a pharmaceutically acceptable carrier and a therapeutically

effective amount of a compound according to one of Claims 1-15 or a pharmaceutically acceptable salt thereof.

17. A method for treating or preventing a thromboembolic disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound according to one of Claims 1-15 or a pharmaceutically acceptable salt thereof.

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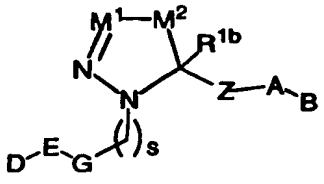

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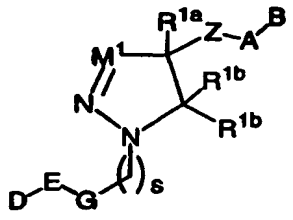

(II)

(57) Abstract

The present application describes disubstituted pyrazolines and triazolines of formulae (I) and (II), or pharmaceutically acceptable salt forms thereof, wherein one of M^1 and M^2 may be N and D may be a variety of N-containing groups, which are useful as inhibitors of factor Xa.

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INTERNATIONAL SEARCH REPORT

Interr[illegible]ication No
PCT/US 99/06310

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D231/06 C07D249/10 C07D401/12 C07D403/12 A61K31/41
A61K31/44 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 98 28269 A (THE DU PONT MERCK PHARMACEUTICAL COMPANY) 2 July 1998 (1998-07-02) the whole document ---	1,15,16
P,A	WO 98 57937 A (THE DU PONT MERCK PHARMACEUTICAL COMPANY) 23 December 1998 (1998-12-23) the whole document ---	1,15,16
P,A	WO 98 57951 A (THE DU PONT MERCK PHARMACEUTICAL COMPANY) 23 December 1998 (1998-12-23) the whole document ---	1,15,16

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
10 September 1999	24/09/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Kyriakakou, G

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 98 57934 A (THE DU PONT MERCK PHARMACEUTICAL COMPANY) 23 December 1998 (1998-12-23) the whole document	1,15,16
A	WO 97 30971 A (THE DU PONT PHARMACEUTICAL COMPANY) 28 August 1997 (1997-08-28) page W	1,15,16
A	WO 97 23212 A (THE DU PONT MERCK PHARMACEUTICAL COMPANY) 3 July 1997 (1997-07-03) the whole document	1,15,16
A	WO 95 14682 A (THE DU PONT MERCK PHARMACEUTICAL COMPANY) 1 June 1995 (1995-06-01) the whole document	1,15,16
A	WO 95 14683 A (THE DU PONT MERCK PHARMACEUTICAL COMPANY) 1 June 1995 (1995-06-01) the whole document	1,15,16
A	US 5 463 071 A (FRANK HIMMELSBACH ET AL.) 31 October 1995 (1995-10-31) the whole document	1,15,16
A	US 5 424 334 A (NORMAN A. ABOOD ET AL.) 13 June 1995 (1995-06-13) the whole document	1,15,16

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/06310

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 17 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see Further INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: claims searched completely: 15 Claims searched incompletely 1-14, 16

In view of the large number and also the wording of the claims presently on file, which render it difficult, if not impossible, to determine the matter for which protection is sought, the present application fails to comply with the clarity and conciseness requirements of Article 84 EPC (see also Rule 29(5) EPC) to such an extent that a meaningful search is impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and concise), namely claim 15. Claims 1-14 and 16 have been only searched as far as specific compounds recited in the examples and closely related homologous compounds are concerned.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

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